THE

VEGETABLE ALKALOIDS.

WITH PARTICULAR REFERENCE TO THEIR CHEMICAL CONSTITUTION.

BY

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FROM THE SECOND FRENCH EDITION.

RENDERED INTO ENGLISH, REVISED AND ENLARGED, WITH THE AUTHOR'S SANCTION,

BY

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PREFACE.

SINCE the appearance in 1897 of the second edition of Prof. Amé Pictet's work, "La Constitution Chimique des Alcaloides Végétaux," marked advances have been made in our knowledge of the alkaloids.

The chemistry of xanthine, caffeïne, theobromine, etc., has attained a certain completeness of development in the recognition of their common relation to purine and in the synthesis of the latter. The constitution of nicotine has been established by its synthesis and three new alkaloids have been isolated from the tobacco-plant (Pictet). Our conceptions regarding the jaborandi alkaloids have been completely revolutionized. The extensive investigations of Ladenburg, Merling, and Willstätter have been brought to a brilliant conclusion in the complete synthesis of atropine, atropamine, belladonnine, inactive cocaïne, and tropacocaïne. Our knowledge regarding the constitution of morphine and codeïne has been so far increased that probably within a short time the synthesis of these two alkaloids will be realized.

These advances have precluded a simple translation of the French edition and have necessitated the complete rewriting of several chapters and the revision of the entire work. It is believed that the present English edition fairly sets forth the latest conceptions regarding the constitution of the more important vegetable alkaloids.

It may be noted that Prof. Pictet's work on the alkaloids was rendered into German in 1900 by Wolffenstein and that a Russian edition is in process of preparation.

H. C. BIDDLE.

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ABBREVIATIONS.

A	Liebig's Annalen der Chemie und Pharmacie.
A. ch.	Annales de chimie et de physique.
Am. Chem. Jour....	American Chemical Journal.
A. Pharm.........	Archiv der Pharmacie.
B.	Berichte der deutschen chemischen Gesellschaft.
Bl.	Bulletin de la Société chimique de Paris.
C. r.	Comptes rendus des séances de l'Académie des Sciences.
G	Gazzetta chimica Italiana.
J.	Jahresbericht über die Fortschritte der Chemie.
J. pr.	Journal für praktische Chemie.
M	Monatshefte für Chemie.
Proc. Soc.	Proceedings of the Chemical Society.
R	Recueil des travaux chimiques des Pays-Bas.
Soc.	Journal of the Chemical Society.
Ztschr. anorg. Chem.	Zeitschrift für anorganische Chemie.

THE VEGETABLE ALKALOIDS.

INTRODUCTION.

TAKEN in its etymological sense the word *alkaloids* may serve to designate all organic substances which possess basic properties; some authors, indeed, have thus used the term. In general, however, its application is limited to those organic bases which are formed in the organism of the plant. A distinction is in this way drawn between basic compounds which we find in nature and those which are prepared solely in the laboratory. The alkaloids, then, do not form a well-defined group in a rational classification of organic compounds, since such a classification would be based on chemical constitution and not upon the source from which they were derived.

An attempt was made by Königs in 1880 to develop a rational classification of the bases found in plants. Investigations on the constitution of these substances showed that, if not all, at least a large number of them yielded pyridine as the ultimate product of their decomposition. It was natural, then, to infer that they were derivatives of this base, just as the aromatic compounds are derivatives of benzol.

Königs suggested that the term alkaloids be reserved for those natural bases which are pyridine derivatives.

The proposal at first met the hearty approval of chemists; it afforded a strictly scientific classification of an important group of organic substances, and this advantage appeared at the time

to afford compensation for the necessity of excluding from the group such bases as caffeïne, choline, betaïne, sinapine, muscarine, etc., which do not contain the pyridine nucleus.

Through later numerous and important investigations on the natural bases, however, the number of those which are not derivatives of pyridine has been greatly increased. Most important among those to which the classification of Königs would deny the name of alkaloid is morphine, the first substance, indeed, which received this name. Further investigation has shown, moreover, that of the basic derivatives of the same plant some may be derivatives of pyridine and others not. Finally, the natural bases of complicated structure, whose constitution is not yet fully known, appear to be only in part derivatives of pyridine.

It seems necessary, therefore, to return to the original significance of the word alkaloid and to apply it without distinction to all natural organic bases, whatever may be their constitution.

We shall then consider that the expressions *vegetable alkaloids* and *vegetable bases* are identical in meaning and that they include all those substances which are directly obtained from the plant and which are able to unite with acids to form salts.

The history of alkaloidal chemistry begins with the early part of the last century. In 1803 Derosne in Paris obtained from opium a crystalline substance which he called *opium-salt*, and which must have been a mixture of morphine and narcotine. The basic properties of this opium-salt he ascribed to an impurity arising from the alkali used in the purification.

The following year Seguin likewise examined morphine, but attached no significance to the observed alkaline reaction of his preparation.

The honor of discovering the first vegetable base and of recognizing its basic character rests with Sertürner, an apothecary of Hanover. Without knowing of the work of Derosne and Seguin, he in 1806 announced that he had obtained from opium a crystalline body which was of basic character, united with acids to form salts, and in the opium was in combination with a special acid.

The discovery of Sertürner remained at first almost unnoticed. It was at that time believed that plants were able to produce only acids, or bodies of neutral reaction. A second publication was required to attract the attention of chemists to this new subject. This publication appeared in 1817 and bore the title "Ueber das Morphium, eine neue salzfähige Grundlage und die Mekonsäure als Hauptbestandtheile des Opiums."

In this article Sertürner definitely characterizes morphium as a vegetable alkali and compares its behavior with that of ammonia.

These exact results awakened interest; it was thought that other plants which possessed marked physiological activity might contain, as active principle, substances analogous to morphium. Many investigations were instituted, with the result that during the years 1817–1835 the most important alkaloids were isolated.

The following is a chronological list of their discovery:

1817.	Narcotine,	by Robiquet
"	Emetine,	" Pelletier and Magendie.
1818.	Veratrine,	" Meissner.
"	Strychnine,	" Pelletier and Caventou.
1819.	Brucine,	" " " "
"	Piperine,	" Oersted.
1820.	Caffeïne,	" Runge.
"	Cinchonine	" Pelletier and Caventou.
"	Quinine,	" " " "
"	Solanine,	" Desfosses.
1825.	Sinapine,	" Henry and Garot.
1826.	Corydaline,	" Wackenroder.
"	Berberine,	" Chevallier and Pelletan.
1828.	Nicotine,	" Posselt and Reimann.
1829.	Aricine,	" Pelletier and Corriol.
"	Sanguinarine,	" Dana.
1830.	Curarine,	" Roulin and Boussingault.
1831.	Conine,	" Geiger.
"	Atropine,	" Geiger and Hesse.

1832.	Codeïne,	by Robiquet.
"	Narceïne,	" Pelletier.
1833.	Quinidine,	" Henry and Delondre.
"	Aconitine,	" Geiger and Hesse.
"	Colchicine,	" " " "
"	Hyoscyamine,	" " " "
1835.	Thebaïne,	" Pelletier and Thiboumery.

The composition of these substances was established by numerous analyses, the most of which we owe to Liebig, Gerhardt, Regnault, and Laurent.

Since 1835 the number of newly discovered alkaloids has increased year by year; to-day we have more than two hundred vegetable bases, which have been fully purified, carefully described and analyzed. In the case of a large number we have learned much regarding the structure of the molecule, and in many instances have succeeded, indeed, in effecting the complete synthesis of the base—the best test of the accuracy of our present conceptions regarding the constitution of the alkaloids.

The complicated structure of the alkaloids first discovered rendered a study of their constitution very difficult. Berzelius explained their basic character by assuming that they held ammonia attached to an indifferent group—to a hydrocarbon or an organic oxide. Others, again, supposed that the nitrogen was united with oxygen, or that it occurred in a form like that of cyanogen.

It remained for Liebig to afford the correct solution. He considered these bases as ammonia in which a hydrogen atom was replaced by an organic radical.

The classical investigations of Wurtz and of Hofmann, which led (1848) to the discovery of the artificial organic bases, fully confirm this view. It was recognized that the artificial as well as the natural bases were partly or completely substituted ammonias. Application to the alkaloids was now made of the reactions, through which Hofmann had learned to distinguish

the four classes of organic bases, and it was found that almost all the alkaloids are tertiary bases.

These investigations found strong support and extension from an unexpected quarter.

In 1834 Runge obtained from coal-tar a basic substance, C_9H_7N, which he named *leucol.* Some years later (1846–1851) Anderson discovered in "Dippel's oil," which results from the dry distillation of bones, a homologous series of volatile bases, of which the first member, of the formula C_5H_5N, received the name *pyridine.* At about the same time it was shown that coal-tar also contained this series of pyridine bases in addition to leucol and a higher homologue of the latter, *iridoline.*

All these substances closely resembled one another; they appeared to constitute a distinct group of organic bases, which were clearly different from the amines of the fatty and of the aromatic series.

We should scarcely expect to find any relation between these bases of pyrogenetic origin and the vegetable alkaloids. The very first investigations, however, which were instituted to determine the constitution of the latter led to this result.

As early as 1842 Gerhardt from the distillation of cinchonine with caustic potash had obtained a peculiar base, which he named *quinoline;* later (1855) Williams found that in this reaction still other basic substances were formed, and among these one of the formula $C_{10}H_9N$, *lepidine.* Closer study of these bases now showed that quinoline was identical with leucol, and lepidine with iridoline.

This observation regarding the relation of the alkaloids to the pyridine bases was soon followed by others. Huber (1867), Wilm and Caventou (1873), Weidel (1874), and more recently Vongerichten, Bernheimer, and Goldschmiedt have shown that by the oxidation of nicotine, cinchonine, quinine, berberine, narcotine, sparteïne, and papaverine there are formed acids which on distillation with lime yield pyridine. Furthermore, piperidine, a decomposition-product of piperine, was recognized by Königs (1879) to be the reduction-product of pyridine. Norhy-

drotropidine (from atropine), nicotine, sparteïne, and the chief alkaloids of the cinchona-barks, when distilled with lime, or zinc-dust, gave rise to homologues of pyridine, some of which were identified with certain members from Anderson's series.

The simple relation subsisting between the pyridine and quinoline bases was established, partly by the synthesis of these bases (Königs, 1879), partly by the direct transformation of quinoline into pyridine (Hoogewerff and van Dorp).

Thus from various sides and in different ways it was shown that the greater number of the alkaloids were derivatives of pyridine. At the same time it was recognized that this relation was not universal, but that there were many alkaloids which could not be correlated with this base. Caffeïne and theobromine, already at that time subjects of important investigations, possessed a constitution which was in no way related to pyridine, but which appeared to classify them with the derivatives of uric acid. Betaïne and muscarine together with choline and sinapine formed a special group of quaternary bases, which were closely related to the amines of the fatty series. Further, the weak bases, leucine and glutamine, which had already been noted as decomposition-products of albuminoid matter and which had been found in numerous plants, belonged undoubtedly to the amido-acids of the fatty series, the asparagine group.

Although, as we see, not all the alkaloids belong to the pyridine series, yet the number falling under such classification was sufficiently large to confer particular interest upon the study of the pyridine bases obtained from coal-tar. This study was undertaken with enthusiasm and led to most important results.

At the time when, under the influence of the stimulating benzol hypothesis of Kekulé, the chemistry of the aromatic derivatives had received a powerful impetus for advancement, Körner (1869) offered a similar conception for the pyridine series.

According to this, pyridine is a benzol in which one of the CH groups is replaced by the triatomic nitrogen atom and the structure of the pyridine nucleus is in all points comparable with that of the benzol nucleus. In the same way, quinoline is to be

regarded as a naphthalene one of whose rings has experienced a like modification.

This hypothesis of Körner was the starting-point for further investigations in the pyridine series. Great numbers of pyridine and quinoline derivatives were prepared, their constitution established, their position in homologous series and their isomeric relations determined; new processes of synthesis were elaborated.

The discovery of acridine by Graebe and Caro in 1870 and that of isoquinoline by Hoogewerff and van Dorp in 1885 brought to a certain completeness these investigations in the pyridine series. Thus within a few years (1870–1885), in addition to the fatty and the aromatic series, there had arisen a third great class of organic substances.

As the investigations in the domain of the artificial pyridine bases were extended, the relations existing between these derivatives and the natural alkaloids became ever clearer. The work of Hofmann and Ladenburg on conine, of Jahns on trigonelline and on the bases of the betel-nut palm, that of Goldschmiedt, of Freund, of Roser, of Perkin on papaverine, hydrastine, narcotine, and berberine, established the constitution of all these bases and at the same time determined their position in the system of pyridine derivatives.

Still other nitrogenous rings have been found in the alkaloids; the oxazine ring in morphine (Knorr), the pyrrolidine ring in hygrine (Liebe mann) and in nicotine (Pinner), and the glyoxaline ring in pilocarpine and isopilocarpine (Jowett, Pinner).

An interesting ring system, resulting from the union of a reduced pyridine with a pyrrolidine nucleus, is found in cocaïne and atropine. The synthesis of this system has been recently effected by the brilliant investigations of Willstätter.

Further research in the chemistry of the alkaloids will doubtless reveal nitrogenous rings of still different types.

One of the great aims which is constantly held in view in studying the constitution of the alkaloids is their synthesis; this, indeed, is the crucial test of the correctness of our views regarding

their structure. Also in this direction considerable success has been attained. If we disregard the two bases, choline and betaïne, which belong to the group of the fatty amines and whose synthesis was effected by Wurtz (1857) and Liebreich (1869), and consider only the alkaloids of cyclical structure, then the honor rests with Ladenburg of having first effected the complete synthesis of such an alkaloid; in 1886 he succeeded in building up from the elements conine, the chief alkaloid of the hemlock.

The same year Hantzsch prepared the methyl-betaïne of nicotinic acid, and this was shown by Jahns to be identical with trigonelline. Since then still other alkaloids have been synthesized: arecaïdine and arecoline by Jahns (1891); piperine by Ladenburg and Scholtz (1894); the bases of the xanthine group, xanthine, caffeïne, theobromine, and adenine by Fischer (1895–1898); atropine, atropamine, belladonine, and inactive cocaïne by Willstätter (1901, 1902); and nicotine by Pictet (1903).

This work is divided into two parts. The first part gives a rapid review of the *artificial derivatives of pyridine.*

The chief data which we have in regard to the constitution of a large number of alkaloids rest upon investigations concerning the constitution of simple pyridine derivatives, into which these alkaloids are converted by their decomposition. Consequently it seems to us best to discuss first the structure of these derivatives and to indicate the methods which have been employed in determining their constitution. In this first part, however, we shall not lose sight of our chief object, the study of the constitution of the vegetable alkaloids, and we shall therefore consider only those artificial derivatives which in their mode of formation, in their molecular structure, or in any other important way are closely related to the natural bases.

In the second part we shall seek to gather together systematically the experimental results which have thus far been derived from the study of the chemical constitution of the natural

alkaloids, and to discuss the theoretical conclusions which have been drawn from these results. No attempt will be made to present a complete monograph of the vegetable alkaloids; we shall not consider in detail either their physiological or physical properties, nor shall we present the specific tests employed in detecting the natural bases. Attention will be fixed rather on the purely chemical behavior of the alkaloids and the bearing of this on their chemical constitution.

FIRST PART.

ARTIFICIAL BASES CLOSELY RELATED TO THE NATURAL ALKALOIDS.

CHAPTER I.

PYRIDINE.

PYRIDINE was discovered by Anderson [1] in 1851 in bone-oil. It is found here accompanied by a number of its homologues. In addition to its production by the dry distillation of bones, it is also formed in the distillation of bituminous coal,[2] lignite, peat, wood, and various bituminous shales.[3] It has been found further in the ammoniacal liquor of gas-works, in fusel-oil, in crude petroleum, and in yellow paraffine oil. At present it is obtained chiefly from coal-tar.

Pyridine is also formed from a number of the alkaloids as nicotine, trigonelline, sparteïne, cinchonine, pseudopelletierine, and derivatives of narcotine when these are highly heated, treated with alkalies, or distilled with zinc-dust. Of theoretical importance is its preparation from piperidine by oxidation. It is obtained, lastly, by the distillation of the calcium salts of various pyridine carboxylic acids, which form the oxidation-products of quinoline, isoquinoline, and a large number of the natural alkaloids.

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[1] Anderson, *Transactions of the Royal Society of Edinburgh*, **20**, 251.
[2] Thenius, J., 1861, 500.
[3] Williams, J., 1854, 492.

Pyridine, C_5H_5N, is a colorless liquid of penetrating odor. It is miscible in all proportions with water, alcohol, and ether. The boiling-point of pyridine is 114°.5, and its density is a little less than that of water.

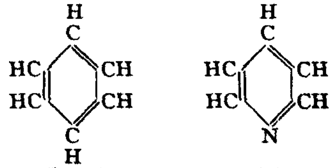
It is a tertiary base, which when reduced with sodium is converted quantitatively into the secondary base, piperidine. When strongly heated with hydriodic acid it is decomposed into ammonia and normal pentane:[4]

$$C_5H_5N + 10H \rightarrow NH_3 + C_5H_{12}.$$

Towards oxidizing agents pyridine exhibits remarkable stability. Chromic acid, potassium permanganate, and nitric acid do not affect the base at any temperature; concentrated sulphuric acid begins to act only at about 300° with the formation of a pyridine sulphonic acid; the halogens yield substitution-products with the greatest difficulty.

Constitution of Pyridine.—The great stability of pyridine, further the analogy which appeared between its derivatives and the corresponding derivatives of the benzol series, particularly in the cases of isomerism, led Körner[5] in 1869 and shortly afterwards also Dewar[6] to assign to the base a constitution similar to that of benzol. They considered the molecular structure to be that of a closed ring composed of five atoms of carbon and one of nitrogen.

According to this assumption pyridine appears as a benzol in which the triatomic CH group is replaced by an atom of nitrogen:



Benzol Pyridine

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[4] Hofmann, B. 16, 586.

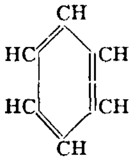
[5] Körner, *Giornale dell' Academia di Palermo*, 1869.

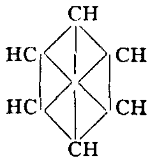
[6] Dewar, *Zeitschrift für Chemie*, 1871, 117.

Körner's hypothesis found much support in a large number of the syntheses in the pyridine series, particularly in the synthesis of pyridine itself, and it is to-day quite generally accepted. This formula for pyridine explains in a thoroughly satisfactory way the reactions of the pyridine series as well as a plane formula can do.

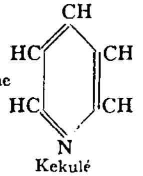
Pyridine is an unsaturated compound. The nitrogen and each of the five carbon atoms possess a free valence. These six free valences unless otherwise attached must mutually compensate one another just as in the benzol ring. To represent these relations many formulæ have from time to time been proposed, of which, however, to-day only the formulæ of Kekulé and Claus need be taken into account. To these, in the case of pyridine, is to be added a third formula of Riedel's,[7] which cannot be considered for the entirely symmetrical benzol ring.

Benzol

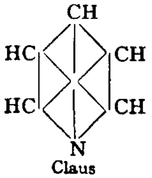




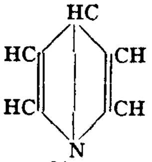
Pyridine



Kekulé

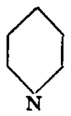


Claus



Riedel

It is not our intention here to discuss these three formulæ, for and against which much may be said. In the succeeding chapters the scheme following will be used to represent the pyridine nucleus:



[7] Riedel, B. 16, 1609.

Syntheses of Pyridine.—Pyridine may be synthesized in many ways, among which the following are mentioned:

1. By the distillation of ethylallylamine over lead oxide heated to 400°–500°:[8]

$$CH_3—CH_2—NH—CH_2—CH=CH_2+3O \rightarrow C_5H_5N+3OH_2.$$

2. By conducting a mixture of acetylene and hydrocyanic acid through a red-hot tube:[9]

$$2C_2H_2+CNH \rightarrow C_5H_5N.$$

This synthesis is analogous to the preparation of benzol from acetylene by Berthelot.

3. By passing a mixture of ammonia and alcohol vapor through a brightly glowing hot tube.[10]

4. From yrrol by heating this base with methylene iodide and sodium methylate to 200°:[11]

$$C_4H_5N+CH_2I_2+2NaOCH_3 \rightarrow C_5H_5N+2NaI+2CH_3OH.$$

5. By heating glycerine with ammonium sulphate.[12]

Some syntheses of pyridine in which it occurs as a side-product in other reactions will be considered with these reactions.

All the known syntheses of pyridine, however, give but poor yields, so that the only source from which it can be obtained in quantity is coal-tar. From this it is readily separated, together with its homologues, by treatment with sulphuric acid. The pyridine bases are freed from the acid solution by the action of an alkali, dried, and finally purified by repeated fractional distillation.

Any aniline present is converted by oxidation into aniline black and in this way removed from the pyridine derivatives.

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[8] Königs, B. **12**, 2344.

[9] Ramsay, B. **10**, 736; Phil. Mag., 1876, 270; 1877, 241.

[10] Monari, J. 1884, 924.

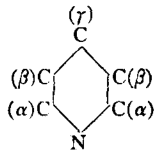
[11] Dennstedt and Zimmermann, B. **18**, 3316.

[12] Stoehr, J. pr. **43**, 153.

Substitution-products of Pyridine.—By replacing any one of the five hydrogen atoms in the pyridine ring with another monatomic atom or radical are formed the substitution-products of pyridine. The study of these derivatives has done much to confirm the hypothesis of Körner.

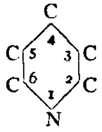
It is fully established by experiment, indeed, that the place-isomerism which is found in the pyridine series is exactly analogous to that in the benzol series.

In representing this isomerism of the pyridine ring the prefixes ortho, meta, and para are not used as in the case of similar aromatic derivatives. In their place are employed the first letters of the Greek alphabet, α, β, and γ:



Pyridine

Less frequently numbers are used as follows:



In the pyridine, as distinguished from the benzol series, there are possible three monosubstitution-products (α, β, γ). By the entrance of several substituents of the same kind the following isomers may be obtained:

6 Disubstitution products ($\alpha\beta$, $\alpha\gamma$, $\alpha\beta'$, $\alpha\alpha'$, $\beta\gamma$, $\beta\beta'$).
6 Trisubstitution " ($\alpha\beta\gamma$, $\alpha\beta\beta'$, $\alpha\beta\alpha'$, $\alpha\gamma\beta'$, $\alpha\gamma\alpha'$, $\beta\gamma\beta'$).
3 Tetrasubstitution " ($\alpha\beta\gamma\beta'$, $\alpha\gamma\beta'\alpha'$, $\alpha\beta\beta'\alpha'$).
1 Pentasubstitution product ($\alpha\beta\gamma\beta'\alpha'$).

When the entering groups are unlike the number of isomers increases rapidly. With four different substituents, for example, there are theoretically possible 120 isomeric derivatives.

The nitro-, sulpho-, and halogen-derivatives of pyridine are formed by direct substitution with difficulty or not at all. These derivatives also have not attained such importance as have the corresponding members in the benzol series. This is due in part, at least, to the fact that the pyridine ring lacks the valuable chromophorous properties which distinguish the benzol ring. Since further these substitution-products of pyridine are only remotely connected with the natural alkaloids, we will discuss them here but briefly.

Chlorpyridines.—The three monochlorpyridines theoretically possible are all known. Two, the α- and γ-derivatives, are obtained by the action of phosphorus pentachloride on the corresponding oxypyridines. The third, β-chlorpyridine, is formed on treating potassium pyrrol with chloroform, or carbon tetrachloride:[13]

$$C_4H_4NK + CHCl_3 \rightarrow C_5H_4ClN + KCl + HCl.$$

Di- and tri-chlorpyridines are also known.

Brompyridines.—Of the three isomers only one is as yet known, β-brompyridine. It is produced by heating pyridine hydrochloride with bromine to 200°.[14] The position of the bromine atom in this compound has been determined by Weidel and Blau.[15] By treating the brompyridine with alcoholic potash they converted it into ethoxypyridine, which when saponified with hydriodic acid yielded β-oxypyridine.

The same brompyridine is formed also from potassium pyrrol and bromoform.[16]

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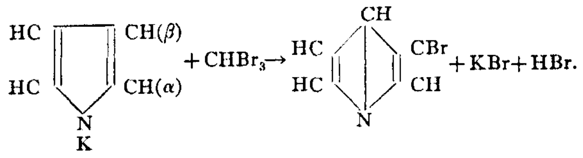
[13] Ciamician and Dennstedt, B. 14, 1153; 15, 1172.
[14] Hofmann, B. 12, 998.
[15] Weidel and Blau, M. 6, 651.
[16] Ciamician and Dennstedt, B. 14, 1153; 15, 1172.

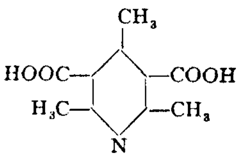
In this reaction consequently the carbon atom of the bromoform enters between the α- and β-carbon atoms of the pyrrol:



This synthesis, which presents a very interesting transition from the pyrrol to the pyridine series, can be generalized. We saw above that in the same way by using chloroform we could obtain chlorpyridine, and by employing methylene iodide we could synthesize pyridine itself.

β-Brompyridine is a colorless liquid, of specific gravity 1.64, boiling-point 169°–170°.

A *dibrompyridine* is formed at the same time with β-brompyridine when the hydrochlorides of pyridine or piperidine[17] are treated with bromine. Further, it is formed from the hydrobromide of tropidine[18] under the action of bromine and from dibromapophylline (a decomposition-product of narcotine) when this is heated with concentrated hydrochloric acid to 210°.[19] In this dibrompyridine the two bromine atoms are in the ββ′ position. This is shown in its formation from symmetrical trimethylpyridine dicarboxylic acid:



by treating this substance with bromine in neutral solution. Both carboxyl groups are replaced by bromine. The dibrom-

[17] Schotten, B. 15, 427.
[18] Ladenburg, B. 15, 1140; A. 217, 74.
[19] Vongerichten, B. 14, 2834; A. 210, 79.

trimethylpyridine thus obtained is then oxidized with potassium permanganate to dibrompyridine tricarboxylic acid, which is finally converted into dibrompyridine by heating with lime (elimination of carbon dioxide).[20]

Dibrompyridine is a solid, well-crystallized substance, melting-point 110°, boiling-point 222°.

A tribrompyridine of unknown constitution melting-point 167–168°, is formed, according to Willstätter, when tropinone is oxidized with bromine.[21]

Iodpyridine.—γ-Iodpyridine is formed by heating γ-chlorpyridine with excess of hydriodic acid for eighteen hours at 145°. Its melting-point is about 100°.[22]

Amidopyridines.—The three isomers have recently been prepared from the amides of the corresponding pyridine monocarboxylic acids by the action of bromine and potassium hydroxide according to the reaction of Hofmann Further, they are formed from the amidopyridine monocarboxylic acids when the carbon dioxide is eliminated by heat.

According to Curtius and Mohr, β-amidopyridine can also be obtained from the hydrazide of nicotinic acid,

$$C_6H_5N—CONHNH_2.$$[23]

α-Amidopyridine melts at 56° and boils at 204°.
β- " " " 64° " " " 250–252°.
γ- " has not as yet been obtained pure in the free condition.

The amidopyridines are easily soluble in water; physiologically they behave as strong poisons.

In general the amidopyridines in their chemical properties resemble the amines of the fatty series; β-amidopyridine alone can be diazotized and converted into azo-dyestuffs. β-pyridyl-

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[20] Pfeiffer, B. 20, 1343.
[21] Willstätter, B. 29, 2228.
[22] Haitinger and Lieben, M. 6, 319.
[23] Curtius and Mohr, B. 31, 2493.

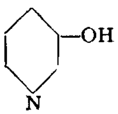
hydrazine is formed by the reduction of β-diazopyridine,[24] while α- and γ-pyridylhydrazine are produced by the action of hydrazine on α- and γ-chlorpyridine.

The Sulphonic Acids of Pyridine.—Pyridine is not affected by fuming sulphuric acid at ordinary temperatures; at about 300°, however, it is converted into β-pyridine sulphonic acid;[25] at the same time there is formed a disulphonic acid (probably ββ').[26]

The sulphonation is aided by the addition of anhydrous aluminum sulphate.[27] The β-position of the group SO_3H is shown by fusing the pyridine monosulphonic acid with potassium cyanide. The acid nitrile obtained is converted by saponification into β-pyridine carboxylic acid (nicotinic acid). The sulphonic acids of pyridine closely resemble the corresponding aromatic derivatives.

Oxypyridines.—A number of derivatives of pyridine are known in which one or more of the atoms of hydrogen are replaced by the hydroxyl group. These may be prepared either by distilling the oxy-acids of pyridine or by the metho s commonly employed in the synthesis of alcohols and phenols (fusion of the sulphonic acids with potassium hydroxide, diazotizing the amines, action of alcoholic potash on the halogen derivatives).

We will consider here only the three monoxypyridines:

β-Oxypyridine  crystallizes in needles melting at 124°.5; it can be distilled without decomposition and gives with ferric chloride a red coloration.

The α- and γ-oxypyridines present a striking example of tau-

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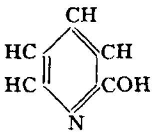
[24] Mohr, B. 31, 2495.

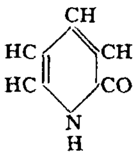
[25] O. Fischer, B. 15, 62; 16, 1183; 17, 763. Königs, B. 12, 2342; 16, 735; 17, 592, 1832.

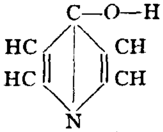
[26] Königs and Geigy, B. 17, 592.

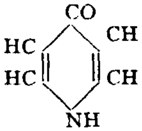
[27] Weidel and Wurman, M. 16, 751.

tomerism. While the β-oxypyridine, as is shown by all its reactions, evidently possesses a hydroxyl structure, the isomeric α- and γ-forms behave sometimes as true hydroxides and sometimes as ketones, assuming, in the latter case, the character of secondary bases (pyridones). It is necessary to consider in these derivatives that one hydrogen atom is highly mobile, attaching itself at one time to the oxygen atom and at another to the nitrogen:


α-Oxypyridine


α-Pyridone


γ-Oxypyridine


γ-Pyridone

This tautomerism appears clearly in the preparation of the esters of the oxypyridines. There are obtained according to the conditions of the experiment either the ordinary ethers with the group —O—R, or nitrogen derivatives with the group =N—R.[28]

α-Pyridone crystallizes in small colorless needles which melt at 107° and distil at 280–281°. With iron chloride it gives a red coloration.

γ-Pyridone forms hexagonal plates which contain one molecule of water. It melts in the anhydrous condition at 148°.5 and boils above 350°; by iron chloride it is colored yellow.

The three oxypyridines are easily soluble in water; they possess only weakly basic properties; on distillation with zinc-dust they are reduced to pyridine.

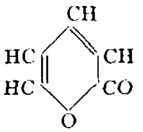
It is necessary to call particular attention to a method of forming the pyridones from the pyrone derivatives, since it throws

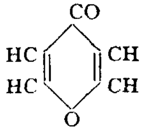
[28] von Pechmann, B. 24, 3144; 28, 1624.

some light on the formation of the alkaloids in the organism of the plant.

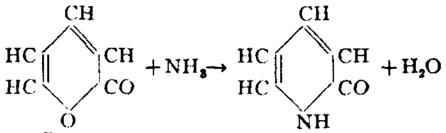
By the name pyrone is indicated a special class of unsaturated ketone-like derivatives, which contain a closed chain of five carbon atoms and one oxgyen atom.

According to the position of this latter to the ketone group are distinguished the α- and γ-pyrones:


α-Pyrone

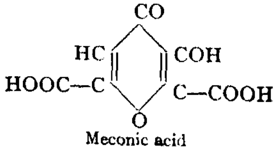

γ-Pyrone

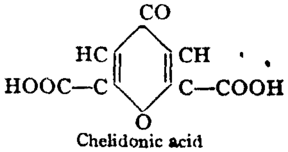
The close relation between the pyrones and the pyridones appears clearly in comparing their structure. By the action of cold ammonia, indeed, the pyrones are converted into the pyridones, an oxygen atom being here replaced by the divalent NH group:


α-Pyrone α-Pyridone

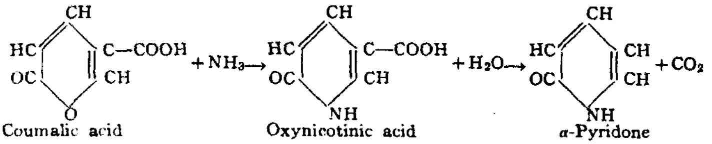
When we recall that plants store up nitrogen in the form of ammonia and when we note this ready conversion of pyrones into pyridones, it would seem that the reaction may play some part in the formation of the alkaloids in the tissues of plants.

Numerous derivatives of the pyrones are known. Those which occur in the vegetable kingdom particularly interest us, such as meconic acid, which is derived from opium, and chelidonic acid, which is found in the herb celandine and in the roots of the white hellebore:


Meconic acid

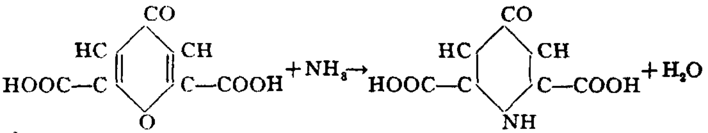

Chelidonic acid

Coumalic acid (α-pyrone carboxylic acid) forms, when treated with ammonia, oxynicotinic acid (α-pyridone-β-carboxylic acid), which is changed by heat into α-pyridone:[29]



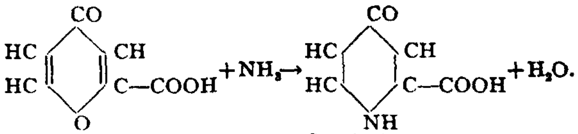
Coumalic acid Oxynicotinic acid α-Pyridone

From chelidonic acid (γ-pyrone dicarboxylic acid) there is formed, by like treatment with ammonia, chelidamic acid (γ-pyridone dicarboxylic acid):[30]



Chelidonic acid Chelidamic acid

By loss of carbon dioxide chelidonic acid may be converted into comanic acid (γ-pyrone monocarboxylic acid). This also with ammonia yields the corresponding pyridone derivative, oxypicolinic acid:[31]



Comanic acid Oxypicolinic acid

Meconic acid (oxy-γ-pyrone dicarboxylic acid) has not as yet been converted into a pyridine derivative. The closely related comenic acid (oxy-γ-pyrone monocarboxylic acid), however, gives with ammonia comenamic acid (dioxypicolinic acid).

Both chelidamic and oxypicolinic acids, when heated above

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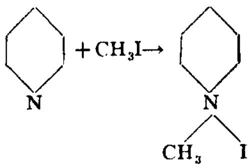
[29] von Pechmann, B. 17, 936, 2384; 18, 317.
[30] Lieben and Haitinger, M. 4, 275; 6, 279.
[31] Ost, J. pr. 27, 257; 29, 57, 378.

their melting-points, are decomposed into carbon dioxide and γ-pyridone

The formation of citrazinic acid (the pyridine acid which is sometimes met in the sugar-beet, see page 157) depends upon a reaction very similar to those just considered.

Addition-products of Pyridine.—Pyridine yields two kinds of addition-products.

1. Like similar tertiary derivatives of nitrogen, the base is able to add alkyl chlorides, bromides, or iodides, thereby, forming compounds of the ammonium type, viz.,



When these quaternary salts are heated to about 300°, they undergo a molecular rearrangement similar to that observed by Hofmann in the case of the alkylated anilines.

The radical attached to the nitrogen migrates to one of the carbon atoms of the ring and there is formed a homologous salt of pyridine. Thus pyridine methiodide, $C_5H_5N{<}^{CH_3}_{I}$, is converted into methylpyridine hydriodide, $CH_3—C_5H_4N{<}^{H}_{I}$.

This reaction, discovered by Ladenburg, has proved very efficient in synthesizing many of the homologues of pyridine.

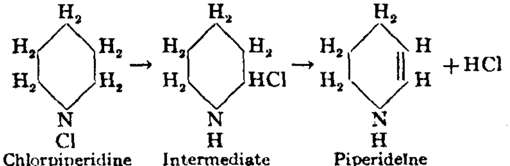
2. Another type of addition-product is derived from saturating the double bonds which are found within the ring itself. Like an unsaturated hydrocarbon, pyridine adds one, two, or three molecules of chlorine, bromine, or hydrogen. The halogen derivatives are in general unstable and as yet little investigated; much more important are the hydrogen addition-products.

Whatever constitutional formula may be assigned to pyridine, it is evident that there should be several isomeric di- and tetra-hydro-derivatives, while the hexahydro-derivative can exist in only one form. No dihydropyridine has yet been prepared in

the pure condition; the tetrahydropyridines (piperideïnes) have been only imperfectly studied; hexahydropyridine (piperidine) has, however, been most thoroughly investigated.

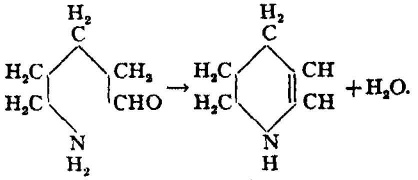
Piperideïnes.—No one has as yet succeeded in preparing a piperideïne by the partial reduction of pyridine. Whatever reagent is employed, it inevitably leads to the completely reduced piperidine. By the reverse process, however, the removal of two atoms of hydrogen from piperidine, a piperideïne has been prepared.[32]

When piperidine is treated with bleaching-powder, there is formed a chlorpiperidine in which the chlorine atom has replaced the hydrogen atom attached to the nitrogen. If this chlor-derivative is now treated with alcoholic potash, hydrogen chloride is split off and there is formed a piperideïne. Since this piperideïne is a secondary base, Lellmann and Schwaderer assume in explanation of the reaction that the chlorine first migrates to the α-carbon atom:



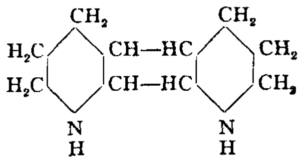
Chlorpiperidine Intermediate product Piperideïne

A piperideïne probably identical with the above has been synthesized by distilling δ-amidovaleraldehyde with caustic potash.[33] The aldehyde is produced from the oxidation of piperidine with hydrogen peroxide. This piperideïne is also a secondary base, and its formation may be expressed as follows:



[32] Lellmann and Schwaderer, B. 22, 1318, 1328.
[33] Wolffenstein, B. 25, 2777.

The piperideïne obtained by either of the above processes is a liquid, easily soluble in water and possessing a stronger basic character than pyridine. It is difficult to determine further its properties with any degree of certainty, since it polymerizes with the greatest ease to a dipiperideïne $(C_5H_9N)_2$, which probably has the constitution



Certain homologues of the piperideïnes have been more thoroughly studied than the piperideïnes themselves, particularly the pipecoleïnes and the coniceïnes, which will be considered later (see pages 35, 135).

Piperidine.—Piperidine was first obtained by Wertheim and Rochleder [34] in 1848 from the distillation of piperine with soda-lime, but they mistook the new substance for aniline. Some years later Anderson [35] and Cahours,[36] working independently of each other, established the formula of the new base as $C_5H_{11}N$, and the latter gave to it the name which it bears to-day.

Piperidine is also formed when piperine is saponified with alcoholic potash (see Piperine):

$$\underset{\text{Piperine}}{C_{17}H_{19}NO_3} + H_2O \rightarrow \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid}}{C_{12}H_{10}O_4}.$$

Johnstone [37] found piperidine occurring in small quantities with piperine in pepper.

Piperidine is a colorless liquid of ammoniacal odor; it is soluble in all proportions in water, alcohol, ether, and benzene. It boils at 105°, and solidifies at −17°; its specific gravity is

[34] Wertheim and Rochleder, A. **54**, 255; **70**, 58.
[35] Anderson, A. **75**, 82; **84**, 345.
[36] Cahours, A. ch. (3) **38**, 76.
[37] Johnstone, *Chemical News*, **58**, 235.

0.88 at 0°; it is a very strong base, readily withdrawing carbon dioxide from the air.

As a secondary base the imide hydrogen atom can be replaced by various groups (alkyl-, amide-, organic, and inorganic acid-radicals, etc.). In this way there may be prepared a large number of interesting derivatives which we are unable to consider here in detail.

The constitution of piperidine remained for a long time unknown. In 1871, Kraut, on treating with moist silver oxide the salts formed by the interaction of the base and chloracetic acid, found that pyridine was produced in small quantities. In 1879, Hofmann,[38] by the action of bromine and water on piperidine at 200–220°, obtained a dibromoxypyridine.

In the same year Königs[39] succeeded in establishing the relation between the two bases by converting piperidine directly into pyridine on heating the former with concentrated sulphuric acid to 300°. At this high temperature the acid acts as an oxidizing agent, and is itself reduced to sulphurous acid:

$$\underset{\text{Piperidine}}{C_5H_{11}N} + 3O \rightarrow \underset{\text{Pyridine}}{C_5H_5N} + 3H_2O.$$

According to later experiments the oxidation of piperidine to pyridine can be effected by heating it with nitrobenzol at 250°,[40] with silver acetate at 180°,[41] or with arsenious acid at 300°.[42] The amount of pyridine formed is, however, small.

The view that piperidine was hexahydropyridine was soon further confirmed by the reduction of pyridine to piperidine. This was accomplished by Königs,[43] in 1881, by heating pyridine with tin and hydrochloric acid:

$$\underset{\text{Pyridine}}{C_5H_5N} + 6H \rightarrow \underset{\text{Piperidine}}{C_5H_{11}N}.$$

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[38] Hofmann, B. 12, 985.
[39] Königs, B. 12, 2341.
[40] Lellmann and Geller, B. 21, 1921.
[41] Tafel, B. 25, 1619.
[42] Königs, B. 30, 1336.
[43] Königs, B. 14, 1856.

Ladenburg[44] showed later that, by the use of sodium and absolute alcohol, the reaction became almost quantitative.

According to Ahrens[45] piperidine may also be prepared by the electrolytic reduction of pyridine in dilute sulphuric acid. Later experiments, however, do not seem to confirm this view.[46]

We know to-day several direct syntheses of piperidine. These all have this in common that they depend on the closing of an open chain of the general form

$$x—CH_2—CH_2—CH_2—CH_2—CH_2—NH—y,$$

by elimination of the elements x and y. The reactions afford additional proof of the constitution.

1. The first of these syntheses was effected by Ladenburg[7] in 1885 in the following way:

Trimethylene cyanide is reduced by the action of sodium upon its alcoholic solution to pentamethylene diamine:

$$CH_2\begin{array}{l}\diagup CH_2—CN \\ \\ \diagdown CH_2—CN\end{array} + 8H \rightarrow CH_2\begin{array}{l}\diagup CH_2—CH_2—NH_2 \\ \\ \diagdown CH_2—CH_2—NH_2\end{array}$$

When the hydrochloride of this base is heated rapidly it is decomposed, giving a mixture of ammonium chloride and piperidine hydrochloride:

$$CH_2\begin{array}{l}\diagup CH_2—CH_2—NH_2.HCl \\ \\ \diagdown CH_2—CH_2—NH_2.HCl\end{array} \rightarrow CH_2\begin{array}{l}\diagup CH_2—CH_2\diagdown \\ \\ \diagdown CH_2—CH_2\diagup\end{array}NH.HCl + NH_4Cl.$$

2. Normal ω-chloramylamine and ω-bromamylamine yield piperidine on being heated with an alkali:[48]

$$CH_2\begin{array}{l}\diagup CH_2—CH_2—Cl \\ \\ \diagdown CH_2—CH_2—NH_2\end{array} + KOH \rightarrow CH_2\begin{array}{l}\diagup CH_2—CH_2\diagdown \\ \\ \diagdown CH_2—CH_2\diagup\end{array}NH + KCl + H_2O.$$

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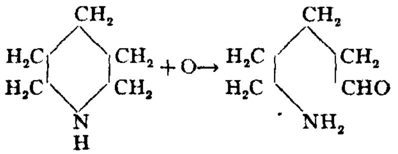
[44] Ladenburg, B. **17**, 156, 388, 513; A. **247**, 1.
[45] Ahrens, *Zeitschrift für Elektrochemie*, **2**, 577.
[46] Pincussohn, Ztschr. anorg. Chem., **14**, 379.
[47] Ladenburg, B. **18**, 2956, 3100.
[48] Gabriel, B. **25**, 421. Blank, B. **25**, 3040.

3. δ-Amidovaleraldehyde, which, it is true, has thus far been obtained only from the oxidation of piperidine, is reconverted into this base when it is reduced with zinc and hydrochloric acid:[49]

$$CH_2\begin{matrix}\diagup CH_2-CHO \\ \\ \diagdown CH_2-CH_2-NH_2\end{matrix} + 2H \rightarrow CH_2\begin{matrix}\diagup CH_2-CH_2\diagdown \\ \\ \diagdown CH_2-CH_2\diagup\end{matrix}NH + H_2O.$$

There is undoubtedly intermediate formation of amidoamyl alcohol which spontaneously loses a molecule of water.

On the other hand, the piperidine ring is somewhat easily broken between the nitrogen and one of the adjacent carbon atoms. Thus, as Wolffenstein has shown, when hydrogen peroxide acts upon the base there is formed among other products δ-amidovaleraldehyde:



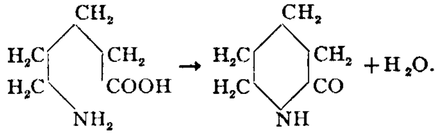
This rupture of the ring is effected still more easily in the case of nitrogen-acyl derivatives of piperidine on oxidation with potassium permanganate. Thus benzoylpiperidine, $C_5H_{10}N(C_6H_5CO)$, yields δ-benzamido-valeric acid;[50] sulphopiperidine, $(C_5H_{10}N)_2SO_2$, δ-sulphamido-valeric acid;[51] and cyanacetylpiperidine, $C_5H_{10}N$-$(COCH_2CN)$, δ-oxalylamido-valeric acid.[52]

The urethane of piperidine behaves somewhat differently toward oxidizing agents. On successive treatment with nitric and hydrochloric acids it is converted into an acid of the formula $C_4H_9NO_2$. This acid has been synthesized by Gabriel,[53] who has shown it to be γ-amidobutyric acid, $NH_2-CH_2-CH_2-CH_2-CO_2H$. It is necessary, then, to assume in the oxidation of

[49] Wolffenstein, B, **25**, 2777; **26**, 2991.
[50] Schotten, B. **16**, 643; **17**, 2545; **21**, 2235.
[51] Töhl and Framm, B. **27**, 2012.
[52] Guareschi, B. **26**, Ref. 92.
[53] Gabriel, B. **23**, 1767.

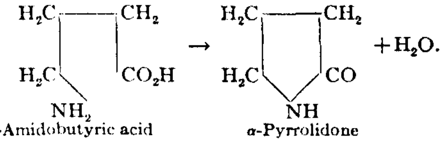
piperyl-urethane that not only the piperidine ring is broken, but also one of its CH_2 groups is eliminated.

Both δ-amidovaleric acid and γ-amidobutyric acid as obtained above show a strong tendency to form an inner anhydride by loss of water, thus again assuming a ring structure. When amidovaleric acid is heated it yields a ketone of piperidine (α-piperidone):



δ-Amidovaleric acid α-Piperidone

α-Amidobutyric acid with the same treatment gives the corresponding pyrrol derivative, α-pyrrolidone:[54]



γ-Amidobutyric acid α-Pyrrolidone

δ-Amidovaleric acid and γ-amidobutyric acid are without any special physiological action; piperidone and pyrrolidone are, however, strong poisons. We have here an interesting connection between chemical constitution and physiological action. Manifestly there exists a close relationship between the ring structure, which is that of almost all the alkaloids, and the action which these bodies have upon the animal organism.

We shall describe finally a method of breaking the piperidine ring which takes place with the simultaneous elimination of nitrogen and which has been used, as we shall see, in determining the constitution of many of the natural alkaloids. This reaction, which we owe to Hofmann, depends upon the following facts:

When piperidine is heated with methyl iodide, the methyl group is substituted for the imide hydrogen and there is formed methylpiperidine, $C_5H_{10}N—CH_3$. This, as a tertiary base, can

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[54] Gabriel, B. 23, 1767.

now add a second molecule of methyl iodide, thus forming a derivative of the ammonium type. This salt, $C_6H_{10}N—CH_3.CH_3I$, is not decomposed by alkalies, but is converted by moist silver oxide into the corresponding hydroxide:

$$C_5HN_{10}(CH_3)_2I \qquad\qquad C_5H_{10}N(CH_3)_2OH$$

Methylpiperidine methiodide — Methylpiperidine methyl hydroxide

Shortly after his discovery of the organic compounds of the ammonium type, Hofmann[55] observed that their hydroxides were decomposed by the action of heat into water, a tertiary amine, and an unsaturated hydrocarbon. Example:

$$\begin{matrix} C_2H_5 \\ C_2H_5 \\ C_2H_5 \end{matrix} \!\!> N < \begin{matrix} C_2H_5 \\ OH \end{matrix} \rightarrow \begin{matrix} C_2H_5 \\ C_2H_5 \\ C_2H_5 \end{matrix} \!\!> N + C_2H_4 + H_2O.$$

Tetraethyl ammonium hydroxide — Triethylamine. — Ethylene.

It was noticed further that if there were one or more methyl groups in the hydroxide, these remained attached to the nitrogen in the tertiary amine.

In 1881 Hofmann[56] applied this reaction to the quaternary derivatives of piperidine and found that their decomposition did not take place according to the general rule which he had established.

Methylpiperidine methyl hydroxide, for example, when subjected to dry distillation yielded no hydrocarbon but only water and a base of the formula $C_7.H_{15}N$, which he named dimethylpiperidine:

$$C_5H_{10}NCH_3.CH_3OH \rightarrow C_5H_9N(CH_3)_2 + H_2O.$$

Methylpiperidine methyl hydroxide — Dimethylpiperidine

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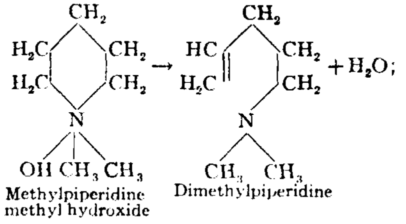
[55] Hofmann, A. **78**, 263.
[56] Hofmann, B. **14**, 494, 659.

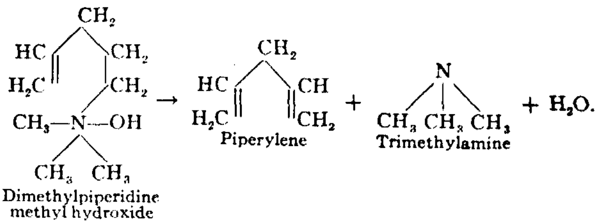
This dimethylpiperidine proved to be a tertiary base. Its addition-product with methyl iodide, on treatment with moist silver oxide, gave a new hydroxide, $C_5H_9N(CH_3)_3OH$. When this hydroxide was subjected to dry distillation, the resulting decomposition conformed with Hofmann's rule. There were formed water, trimethylamine, and an unsaturated hydrocarbon of the formula C_5H_8, piperylene:

$$C_5H_9N(CH_3)_3OH \rightarrow H_2O + N(CH_3)_3 + C_5H_8.$$

Piperylene is a liquid boiling at 42°; as an unsaturated compound, it readily adds four atoms of bromine.

Ladenburg[57] appears to have found the true interpretation of these reactions. He considers that the ring of the methylpiperidine is broken in the distillation of its methyl hydroxide. The two successive phases of the reaction may be represented by the following equations:





Dimethylpiperidine is of considerable importance in that it affords a transition to pyrrolidine-derivatives.[58]

On treatment with hydrogen chloride, there is formed hydrochlordimethylpiperidine (δ-chloramyl-dimethylamine),

[57] Ladenburg, B. **14**, 1346; **15**, 1024; **16**, 2057; A. **279**, 344.
[58] Roser, A. **247**, 62. Merling, A. **264**, 310. Ladenburg, A. **279**, 344.

$CH_3—CHCl—CH_2—CH_2—CH_2—N(CH_3)_2$. When this is warmed it undergoes molecular rearrangement to *n*-α-dimethylpyrrolidine methyl chloride,

$$\begin{array}{l} CH_2—CH(CH_3)— \\ | \\ CH_2—CH_2— \end{array} \!\!\!> N(CH_3)_2Cl.$$

At a still higher temperature the chloride suffers decomposition into *n*-methyl-α-methylpyrrolidine,

$$\begin{array}{l} CH_2—C(CH_3) \\ | \\ CH_2—CH_2— \end{array} \!\!\!> NCH_3$$

and methyl chloride.

CHAPTER II.

HOMOLOGUES OF PYRIDINE

THE homologues of pyridine are derived from this body by the replacement of one or more hydrogen atoms with alkyl radicals. The position of the radical is determined, as in the aromatic series, by oxidation. Side-chains are thus converted into carboxyl groups, while the pyridine ring remains intact. We obtain in this way an acid with one or more carboxyl groups. From the constitution of this acid are determined both the number and the position of the alkyl substituents in the original base.

The homologues of pyridine are found with pyridine in bone-oil and in coal-tar. Anderson[1] (1846–1851) obtained from the distillation of bones the following bases:

Pyridine	C_5H_5N
Picoline	C_6H_7N
Lutidine	C_7H_9N
Collidine	$C_8H_{11}N$
Parvuline	$C_9H_{13}N$

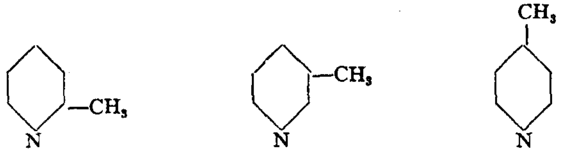
and other higher homologues.

A. THE PICOLINES (Methylpyridines), C_6H_7N.

Anderson described the picoline from bone-oil as a liquid boiling at 130°–140°, not solidifying at − 18°, soluble in all proportions in water and in all its properties resembling pyridine.

[1] Anderson, *Transactions of the Royal Society of Edinburgh*, **16**, 123, 463; **20**, 247; **21**, 219.

In 1879 Weidel[2] and later Ost[3] and Lange[4] showed that the picoline of Anderson's was not a homogeneous product but a mixture of three isomeric bases. They separated the three derivatives from one another through their platinum salts and established their constitution by converting them into the three monocarboxylic acids of pyridine:



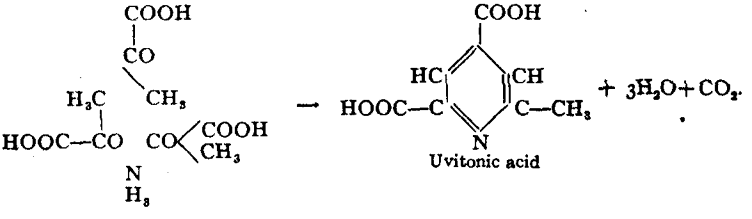
α-Picoline — B.P. 129°; is converted by oxidation into picolinic acid.

β-Picoline — B.P. 142°–143°; is converted by oxidation into nicotinic acid.

γ-Picoline — B.P. 144°–145°; is converted by oxidation into isonicotinic acid.

1. **α-Picoline.**—This with other pyridine bases is formed in the distillation of the sulphate of sparteïne over zinc-dust.[5]

It was synthesized by Böttinger[6] in the following manner: When pyruvic acid, $CH_3COCOOH$, is treated with alcoholic ammonia there is formed a dibasic acid, $C_6H_5N(COOH)_2$, the so-called *uvitonic acid.* According to its constitution, as established by Altar,[7] this substance is α-picoline-γα′-dicarboxylic acid. Its formation by the condensation of ammonia with pyruvic acid may be represented thus:



Uvitonic acid

[2] Weidel, B. 12, 1989; M. 1, 46.
[3] Ost, J. pr. 27, 286.
[4] Lange, B. 18, 3436.
[5] Ahrens, B. 26, 3035.
[6] Böttinger, B. 10, 362; 13, 2032; A. 188, 330; 208, 122.
[7] Altar, A. 237, 182.

On distillation with lime, uvitonic acid loses carbon dioxide and is converted into α-picoline.

α-Picoline is also formed in the general synthesis of Ladenburg by heating pyridine methiodide to 300°.[8]

α-Picoline is distinguished from both its isomers by the ease with which it reacts with ketones and aldehydes.

According to the conditions of the experiment, it forms either hydroxy-derivatives, the so-called *alcamines* (see p. 49), by simply adding itself to the ketone or aldehyde, or compounds with an unsaturated side-chain by subsequent loss of a molecule of water:

$$\underset{\alpha\text{-Picoline}}{C_5H_4N{-}CH_3} + \underset{\text{Formaldehyde}}{CH_2O} \rightarrow \underset{\alpha\text{-Picolyl alcamine}}{C_5H_4NCH_2{-}CH_2OH.}$$

$$\underset{\alpha\text{-Picoline}}{C_5H_4N{-}CH_3} + \underset{\text{Acetaldehyde}}{OCH{-}CH_3} \rightarrow \underset{\alpha\text{-Allylpyridine}}{C_5H_4N{-}CH{=}CH{-}CH_3} + H_2O.$$

This reaction is common to all pyridine and quinoline derivatives which have a methyl group in the α-position.

2. **β-Picoline.**—β-Picoline is obtained in the decomposition of several of the alkaloids. It is formed when strychnine and brucine are heated with lime[9] and when guvacine is distilled with zinc-dust.[10] It is produced also by the pyrogenetic decomposition of nicotine and is found with other pyridine bases in tobacco-smoke.[11]

Several syntheses of β-picoline are known.

It was first obtained by Baeyer[12] in 1870 from the distillation of acrolein-ammonia. This last substance, formed by the interaction of acrolein and ammonia, possesses very probably the following constitution:

$$CH_2{=}CH{-}CH{=}N{-}CH(OH){-}CH{=}CH_2.$$

Under the action of heat, water is eliminated and the chain

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[8] Lange, B. **18**, 3436.

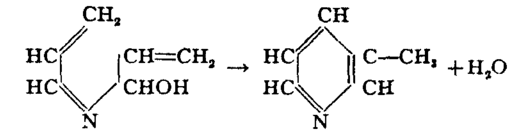
[9] Stoehr, B. **20**, 810, 2727; J. pr. **42**, 399, 415.

[10] Jahns, A. Pharm. **229**, 669.

[11] Vohl and Eulenburg, A. Pharm. **147**, 130. Kissling, *Dingler's polytechnisches Journal*, **244**, 64, 234.

[12] Baeyer, A. **155**, 281.

closed with a simultaneous change in the attachment of one of the hydrogen atoms:



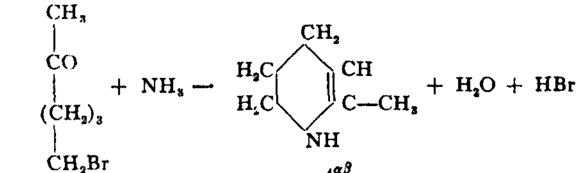
β-Picoline is also formed when gylcerine is heated with acetamide,[13] or ammonium sulphate or phosphate,[14] in the presence of phosphoric anhydride.

In all these modes of formation it is probable that the glycerine is first converted by loss of water into acrolein, which then condenses with ammonia to form the pyridine ring.

3. **γ-Picoline.**—γ-Picoline has been obtained by heating cincholoiponic acid with dilute sulphuric acid to 260–270°.[15] Cincholoiponic acid is an oxidation-product of the cinchona alkaloids. γ-Picoline is formed, further, in large quantities, together with the α-derivative, by the transposition of the methyl group when pyridine methiodide is heated.[16] It has also been prepared by Hantzsch[17] from symmetrical trimethylpyridine (see page 45) by eliminating through oxidation the two methyl groups in the αα'-position.

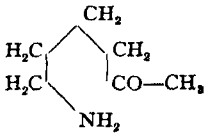
Pipecoleïnes (Tetrahydropicolines), $C_6H_{11}N$.—We possess a good method for preparing one of the several pipecoleïnes theoretically possible.

α-Pipecoleïne is formed by the action of alcoholic ammonia on ω-brombutyl methyl ketone:[18]



[13] Zanetti, *Annali di chimica*, **74**, 13; Hesekiel, B. **18**, 910, 3091.
[14] Stoehr, J. pr. **43**, 153; Schwarz, B. **24**, 1676; Storch, B. **19**, 2456.
[15] Skraup, M. **17**, 365.
[16] Lange, B. **18**, 3436.
[17] Hantzsch, A. **215**, 61.
[18] Lipp, A. **289**, 173.

In this reaction there is probably first produced the unstable intermediate product ω-amidobutyl methyl ketone,



which by loss of water is converted into tetrahydropicoline.

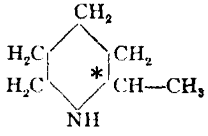
Tetrahydropicoline is a secondary base; it boils at 131–132° (716 mm.).

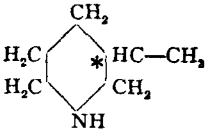
It has been a special object of study because of its close relation to tropine (page 202).

Pipecolines (Methylpiperidines, Hexahydropicolines), $C_6H_{13}N$. —The pipecolines are prepared either by reduction of the three picolines with sodium and alcohol,[19] or by synthetic processes directly analogous to those used in obtaining piperidine.[20]

α-Pipecoline boils at 118–119°, β-pipecoline at 124°, and γ-pipecoline at 127–129°. The boiling-points rise in about the same way in the isomeric pipecolines as in the corresponding picolines.

α- and β-Pipecoline possess an asymmetric carbon atom. These are the first bodies of this class which we have as yet met in this rapid survey of the pyridine derivatives:


α-Pipecoline


β-Pipecoline

According to the theory of Le Bel and van't Hoff these pipecolines should present the phenomena of stereoisomerism and should consequently be separable into their optical isomers. Such a

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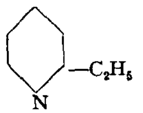
[19] Ladenburg, B. 17, 388; 18, 47, 910; 20, 288; A. 247, 1.
[20] Granger, B. 30, 1060.

separation has been actually accomplished by a fractional crystallization of their bitartrates.[21]

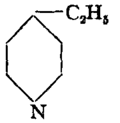
B. THE LUTIDINES, C_7H_9N.

There are theoretically possible nine isomeric lutidines, of which three are ethylpyridines and six dimethylpyridines. Of these the three ethyl and five dimethyl derivatives are known.

α- and γ-Ethylpyridine are formed simultaneously when pyridine ethiodide is heated to 290°:[22]



α-Ethylpyridine
B.P. 148°.5; is converted by oxidation into picolinic acid.



γ-Ethylpyridine
B.P. 164–166°; is converted by oxidation into isonicotinic acid.

The α-derivative is also formed by the distillation of norhydrotropidine[23] (a product of the decomposition of tropine) and of ecgonine[24] over zinc-dust.

β-Ethylpyridine is of considerable importance, since it can be obtained as a decomposition-product from several of the alkaloids. It was found in 1855 by Williams[25] in the distillation of cinchonine and quinine with potassium hydroxide; this observation was later confirmed by Wischnegradsky[26] and Oechsner.[27] Königs[28] noted its formation in the distillation of meroquinine with zinc-dust. Other investigators[29] have obtained the base by subjecting cincholoipone to the same treatment.

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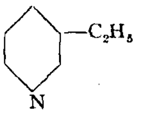
[21] Ladenburg, B. **26**, 854, 1069; **27**, 75, 853, 1409; A. **279**, 344.
[22] Ladenburg, B. **16**, 1410, 2059; **18**, 2961; A. **247**, 1.
[23] Ladenburg, B. **20**, 1647.
[24] Stoehr, B. **22**, 1126.
[25] Williams, *Chemical News*, **44**, 307; J. 1855, 594; 1864, 437.
[26] Wischnegradsky, B. **11**, 1253; **12**, 1480.
[27] Oechsner, C. r. **91**, 296; **92**, 413.
[28] Königs, B. **27**, 900.
[29] Weidel and Hazura, M. **3**, 770. Skraup, M. **7**, 517; **9**, 783.

β-Lutidine may also be derived from strychnine and brucine when these alkaloids are heated with lime or caustic potash.[30] It is formed when the vapor of nicotine is conducted through a tube heated to redness,[31] and it is found further in tobacco-smoke.[32]

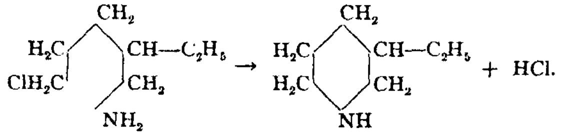
A simple method for the synthesis of β-ethylpyridine is not as yet known. Stoehr[33] states that it is formed in small quantities when glycerine is heated with ammonium phosphate or sulphate.

β-Lutidine is a liquid which boils at 166°. Its constitution is shown by its conversion on oxidation into nicotinic acid:



By the reduction of β-lutidine with sodium and alcohol there is formed β-ethylpiperidine or β-lupetidine.*

This same derivative of piperidine may be prepared by a method first suggested by Gabriel,[34] viz., by heating β-ethyl-ε-chloramylamine with an alkali:



α- and γ-Piperidine have also been obtained from the reduction of the corresponding lutidines:

α-Piperidine,	boiling-point	142–145°.[35]
β- "	"	154–155°.[34]
γ- "	"	155–158°.[35]

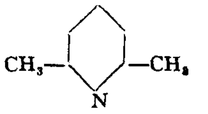
[30] Oechsner, C. r. **95**, 298; **96**, 200, 437. Stoehr, J. pr. **42**, 399, 415.
[31] Cahours and Etard, C. r. **90**, 275.
[32] Vohl and Eulenburg, A. Pharm. **147**, 130.
[33] Stoehr, J. pr. **43**, 153; **45**, 20.
* A nomenclature which has been suggested for the reduced pyridine bases is formed by inserting "pe" between the first and second syllables in the name of the unreduced base: pyridine—piperidine; lutidine—lupetidine, etc.
[34] Günther, B. **31**, 2134.
[35] Ladenburg, B. **17**, 388; **18**, 2961.

α- and β-Piperidine have been separated through the bitartrates into their optical isomers.[36]

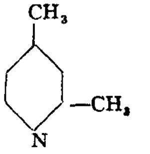
The five dimethylpyridines at present known are found together in the fraction of bone-oil to which Anderson gave the name of lutidine. They have also been obtained from coal-tar.

The separation of these five isomers and the determination of their constitution has particularly engaged the attention of a number of investigators, as Weidel and Herzig, Weidel and Hazura, Ladenburg and Roth, Schulze, Ahrens, Lunge and Rosenberg.[37]

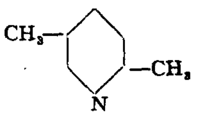
The following constitutional formulæ may now with certainty be assigned these lutidines:



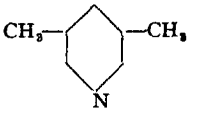
αα'-Dimethylpyridine B.P. 142°–143; is converted by oxidation into dipicolinic acid.



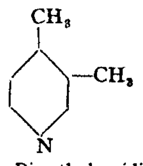
αγ-Dimethylpyridine B.P. 156–157°; is converted by oxidation into lutidinic acid.



αβ'-Dimethylpyridine B.P. 162–167°; is converted by oxidation into isocinchomeronic acid.



ββ'-Dimethylpyridine B.P. 169–170°; is converted by oxidation into dinicotinic acid.



βγ-Dimethylpyridine B.P. 164°; is converted by oxidation into cinchomeronic acid.

A large number of syntheses for these bases are known. We shall, however, refrain from enumerating them, since none of the dimethylpyridines has as yet attained any importance in the study of the constitution of the alkaloids.

[36] Ladenburg, A. 247, 1. Günther, B. 31, 2134.

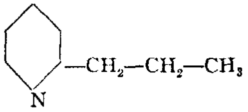
[37] Weidel and Herzig, M. 1, 1. Weidel and Hazura, M. 5, 656. Ladenburg and Roth, B. 18, 913, 1590. Lunge and Rosenberg, B. 20, 127. Ahrens, B. 29, 2996. Schulze, B. 20, 411.

C. The Collidines, $C_8H_{11}N$.

The number of collidines theoretically possible amounts to twenty-two; of these but ten are known:

	Theoretically possible.	Actually known.
Propylpyridines (normal)	3	2
Isopropylpyridines	3	2
Methylethylpyridines	10	4
Trimethylpyridines	6	2

1. α-Propylpyridine.



This base was also called conyrine by Hofmann,[38] who obtained it by distilling conine hydrochloride with zinc-dust:

$$\underset{\text{Conine}}{C_8H_{17}N} \rightarrow \underset{\text{Conyrine}}{C_8H_{11}N} + 6H.$$

Ciamician and Silber[39] found that granatanine hydrochloride subjected to the same treatment also gave conyrine. It is likewise formed when conine is heated to 180° with silver acetate in a solution of acetic acid.[40]

Conyrine is a colorless liquid, boiling at 166–168°. On oxidation it yields picolinic acid; it consequently possesses only one side-chain, and this is in the α-position. Further, since conyrine is not identical with the α-isopropylpyridine synthesized by Ladenburg, it must be regarded as the normal propyl derivative.

When heated with hydriodic acid to 280–300°, conyrine is reduced to α-propylpiperidine, a liquid boiling at 166–167°.[41]

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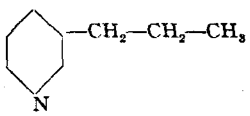
[38] Hofmann, B. **17**, 825; **18**, 109.
[39] Ciamician and Silber, B. **27**, 2850.
[40] Tafel, B. **25**, 1619.
[41] Ladenburg, B. **19**, 439, 2578; A. **247**, 1.

This latter base has also been obtained by the reduction of α-allylpyridine, of α-propionylpyridine,[42] and of γ-coniceïne.[43] It constitutes, as we shall see later (p. 126), the racemic form of conine.

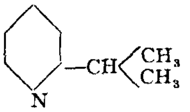
2. β-Propylpyridine.

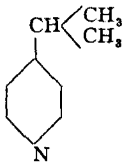


This collidine (boiling-point 170°) is obtained by conducting nicotine through a tube heated to redness.[44] Its constitution is shown by its conversion on oxidation into nicotinic acid.

A collidine probably identical with this β-derivative is found, according to Le Bon and Noël[45] and Eulenburg,[46] in tobacco-smoke.

3. α-Isopropylpyridine. 4. γ-Isopropylpyridine.





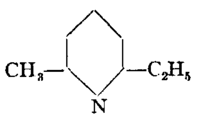
These two bases are formed simultaneously when a mixture of pyridine and isopropyl iodide is heated to 290° (Ladenburg[47]). α-Isopropylpyridine boils at 158–159° and is converted by oxidation into picolinic acid; γ-isopropylpyridine boils at 177–178° and on oxidation yields isonicotinic acid.

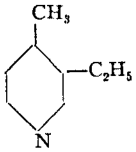
By the action of normal propyl iodide on pyridine at 290°, Ladenburg obtained collidines identical with the preceding in-

[42] Engler and Bauer, B. 24, 2530; 27, 1775.
[43] Lellmann and Müller, B. 23, 680.
[44] Cahours and Etard, C. r. 92, 1079; 96, 275; 97, 1218.
[45] Le Bon and Noël, C. r. 90, 1538.
[46] Vohl and Eulenburg, A. Pharm. 147, 130.
[47] Ladenburg, B. 17, 772, 1121, 1676; 18, 1587; A. 247, 1.

stead of normal propylpyridines, which should apparently be formed. At the temperature of the reaction the propyl radical is converted into the isopropyl. Normal propylpyridines cannot, then, be formed by this general synthesis of Ladenburg.

5. α-Collidine. **6. β-Collidine.**





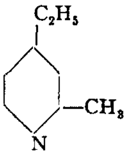
By the fusion of cinchonine with caustic potash there are formed two isomeric collidines which have received the names of α- and β-collidine respectively, and which are to be considered as methylethylpyridines.[48] Brucine with similar treatment gives rise to the same two bases.

α-Collidine (boiling-point 179–180°) is reduced by hydriodic acid to normal octane, and is oxidized by potassium permanganate to dipicolinic acid. From these reactions is determined its constitution.

β-Collidine (boiling-point 195–196°) on oxidation yields successively homonicotinic acid (γ-methyl-β-pyridine carboxylic acid) and cinchomeronic acid (βγ-pyridine dicarboxylic acid). Whence its constitution is as noted above.

β-Collidine has also been obtained by heating meroquinene with hydrochloric acid to 240°.[49]

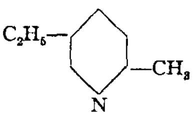
7. α-Methyl-γ-ethylpyridine.



[48] Williams, J. 1885. 550. Oechsner, C. r. **91**, 296; **95**, 298; **98**, 1438; **100**, 806.
[49] Königs, B. **27**, 1501.

This base (boiling-point 169–174°) was prepared by Schultz[50] by heating α-picoline with ethyl iodide to 280–300°. Its constitution is shown by its oxidation to lutidinic acid (pyridine-αγ-dicarboxylic acid). In the synthesis of α-methyl-γ-ethylpyridine there is formed also an isomeric base which is probably α-collidine, although there seems to be considerable difference between their boiling-points. On oxidation this isomer is converted into dipicolinic acid.

8. Aldehydine, or Aldehyde Collidine.



This collidine (boiling-point 173–174°) Ador and Baeyer[51] prepared in 1870 by heating an alcoholic solution of aldehyde-ammonia to 120°:

$$4C_2H_7NO \rightarrow C_8H_{11}N + 4H_2O + 3NH_3.$$

Its constitution was determined by Dürkopf in 1885 as α-methyl-β′-ethylpyridine. With potassium permanganate it is converted first into α-picoline-β′-carboxylic acid and then into isocinchomeronic acid (pyridine-αβ′-dicarboxylic acid).

The formation of aldehydine in the above reaction may be explained as follows:

The aldehyde-ammonia doubtless dissociates into its two constituents. The aldehyde thus set at liberty condenses with a second molecule to crotonaldehyde:

$$CH_3—CH{=}CH—CHO.$$

The latter then reacts with the ammonia with the elimination

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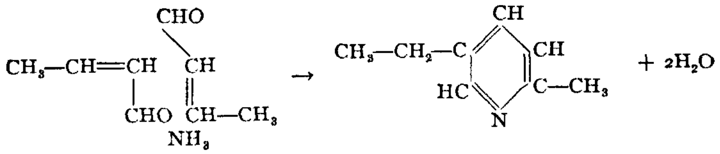
[50] Schultz, B. **20**, 2720.
[51] Ador and Baeyer, A. **155**, 294.

of two molecules of water and the migration of a hydrogen atom, as in the formation of β-picoline (see p. 34):



Since the work of Ador and Baeyer, a large number of other methods for synthesizing aldehydine have become known. The most of these depend on a condensation similar to that just considered. The following may be mentioned as the most important:

The action of ammonia on ethylidene bromide or chloride:[52]

$$4C_2H_4Br_2 + NH_3 \rightarrow C_8H_{11}N + 8HBr.$$

The action of ammonium chloride on glycol[53] or on paraldehyde:[54]

$$4C_2H_6O_2 + NH_4Cl \rightarrow C_8H_{11}NHCl + 8H_2O.$$

The distillation of aldol-ammonia:[55]

$$2C_4H_8O_2NH_3 \rightarrow C_8H_{11}N + 4H_2O + NH_3.$$

The action of phosphoric anhydride on a mixture of paraldehyde and acetamide.[56]

The condensation of aldehyde-ammonia with paraldehyde.[57]

The base is best purified by the method given by Knudsen.[58]

When aldehydine is reduced with sodium and alcohol there are formed two stereoisomeric methylethylpiperidines (copellidine and isocopellidine). Each of these inactive copellidines can be

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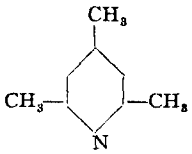
[52] Krämer, B. **3**, 262. Tawildarow, A. **176**, 15.
[53] Hofmann, B. **17** 1905.
[54] Plöchl, B. **20**, 722.
[55] Wurtz, C. r. **95**, 263.
[56] Hesekiel, B. **18**, 3091.
[57] Dürkopf, B. **20**, 444.
[58] Knudsen, B. **28**, 1759.

separated into two optically active forms by crystallization of their bitartrates, so that, in all, six forms appear to exist, four optically active, two inactive.[59] This isomerism is to be explained by the respective positions (cis and trans) of the two side-chains with regard to the plane of the piperidine ring.

9. Symmetrical Trimethylpyridine.



This base (boiling-point 171–172°) is found in coal-tar.[60] It may be synthesized by heating acetone with ammonium chloride, urea,[61] or aldehyde-ammonia.[62]

The most important method of preparing symmetrical trimethylpyridine, however, was developed by Hantzsch[63] in the course of his study of the condensation-products resulting from the interaction of aceto-acetic ester, aldehyde, and ammonia. His study led to a general synthetic method which has proved of the highest value in determining the constitution of many derivatives of the pyridine series.

In 1882 Hantzsch observed that aceto-acetic ester and aldehyde-ammonia easily react with each other at the temperature of the water-bath:

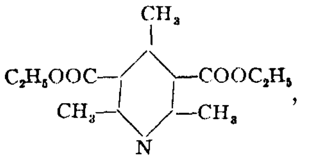
$$\underset{\text{Aceto-acetic ester}}{2C_6H_{10}O_3} + \underset{\text{Aldehyde-ammonia}}{C_2H_7NO} \rightarrow C_{14}H_{21}NO_4 + 3H_2O.$$

A study of the product, $C_{14}H_{21}NO_4$, showed it to be a pyridine derivative, indeed, the ethyl ester of a dihydrocollidine dicarboxylic

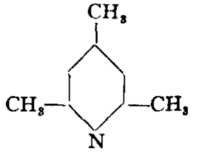
[59] Levy and Wolffenstein, B. 28, 2270; 29, 1959.
[60] Mohler, B. 21, 1006. Ahrens, B. 28, 795.
[61] Riehm, A. 238, 1.
[62] Dürkopf, B. 21, 2713.
[63] Hantzsch, B. 15, 2914; A. 215, 1.

acid. When this was gently oxidized, it lost two atoms of hydrogen and was converted into an ethyl ester of a collidine dicarboxylic acid, which proved to be trimethylpyridine dicarboxylic acid:

$$C_{14}H_{21}NO_4 + O \rightarrow C_5N(CH_3)_3(COOC_2H_5)_2 + H_2O.$$

This ester,  , was then saponified

and, by heating with lime, converted into symmetrical trimethylpyridine ($\alpha\gamma\alpha'$):



On further study Hantzsch found that the above reaction was a general one and that not only acetaldehyde but all aldehydes would condense with aceto-acetic ester and ammonia to form derivatives of pyridine.

The condensation with benzaldehyde proved particularly instructive in affording an insight into the mechanism of the reaction and in determining the position of the side-chains in the derivatives formed.[64]

Benzaldehyde, aceto-acetic ester, and ammonia react according to the following equation:

$$2CH_3—CO—CH_2—COOC_2H_5 + C_6H_5—CHO + NH_3 \rightarrow$$
$$C_5H_2N(C_6H_5)(CH_3)_2(COOC_2H_5)_2 + 3H_2O.$$

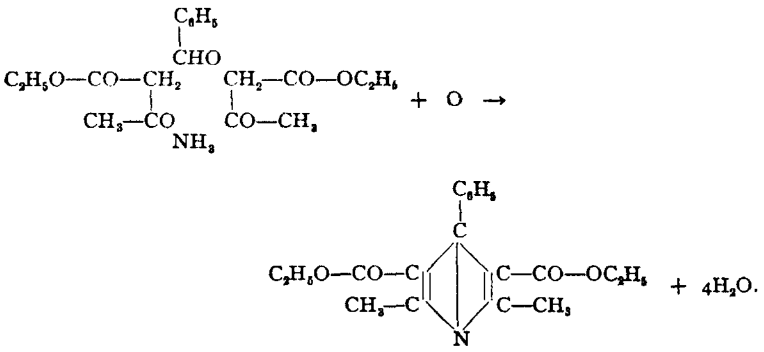
When this reaction-product is oxidized there is formed the ester

[64] Hantzsch, B. 17, 1512, 2903.

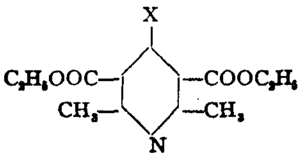
of phenyllutidine dicarboxylic acid, $C_5N(C_6H_5)(CH_3)_2(COOC_2H_5)_2$. This ester is saponified and then oxidized with potassium permanganate, whereby it is converted into the tetracarboxylic acid of a phenylpyridine, $C_5N(C_6H_5)(COOH)_4$. The calcium salt of this acid on distillation yields a phenylpyridine, $C_5H_4N(C_6H_5)$.

Now, this phenylpyridine by the action of stronger oxidizing agents is converted into isonicotinic acid; it is consequently γ-phenylpyridine.

From this Hantzsch concluded that the condensation of benzaldehyde with ammonia and aceto-acetic ester takes place in such a way that the radical of the aldehyde occupies the γ-position with respect to the nitrogen atom. The reaction leading to the formation of the ester of phenyllutidine dicarboxylic acid he accordingly represents as follows:



The general formula for the condensation-product of any aldehyde, X—CHO, may consequently be thus represented:



By condensation with propionaldehyde, isobutyraldehyde,

valeraldehyde and cinnamic aldehyde, Hantzsch and his students[65] have prepared numerous derivatives in which X of the general formula is replaced by the radicals C_2H_5, C_3H_7, C H_9, C_8H_7.

These condensations can naturally be extended in various ways and the products of condensation may, by partial or complete oxidation of the side-chains, by the elimination of carboxyl groups, etc., give rise to a multiplicity of pyridine derivatives. A discussion of these, however, lies beyond the province of this work.

According to the investigations of Beyer[66] and later those of Knoevenagel,[67] the foregoing condensation of Hantzsch may take place in the following phases:

The aldehyde-ammonia acts upon the aceto-acetic ester to form ethylidene-aceto-acetic ester:

$$CH_3CO—CH_2COOC_2H_5 + CH_3CH\Big\langle{}^{OH}_{NH_2} \rightarrow CH_3CO—\underset{\underset{CH—CH_3}{\|}}{C}—COOC_2H_5 + NH_3.$$

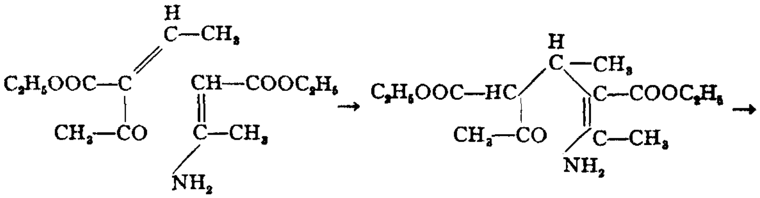
Ethylidene-aceto-acetic ester

The ammonia thus liberated reacts in turn with aceto-acetic ester, giving rise to β-amidocrotonic ester:

$$CH_3\underset{\underset{OH}{|}}{C}{=}CH\cdot COOC_2H_5 + NH_3 \rightarrow CH_3\underset{\underset{NH_2}{|}}{C}{=}CHCOOC_2H_5 + H_2O.$$

β-Amidocrotonic ester

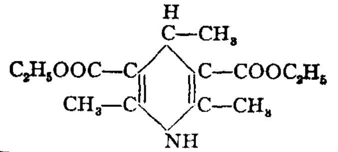
Lastly, the ester of dihydro-collidine dicarboxylic acid is produced by the condensation of ethylidene-aceto-acetic ester and β-amidocrotonic ester:



[65] Michael, A. 225, 121. Voigt, A. 228, 29. Engelmann, A. 231, 1. Epstein, A. 231, 137. Weiss, B. 19, 284, 1305.

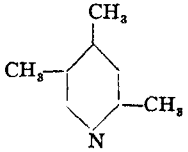
[66] Beyer, B. 24, 1662.

[67] Knoevenagel, B. 31, 738.



Ester of dihydro-collidine dicarboxylic acid

10. *αγβ′*-**Trimethylpyridine.**



This base is found in coal-tar;[68] it boils at 165–168°. Its constitution is shown by its conversion to berberonic acid when oxidized with potassium permanganate.

ALCAMINES, OR ALKINES.

With these names Ladenburg designates compounds which contain both an alcoholic hydroxyl and an amide group. In the pyridine series in particular are thus indicated the derivatives having a hydroxyl in a side-chain.

These bodies are of considerable interest in their relation to the alkaloids, since among the latter are found certain alcamines, as conhydrine and further tropine, a decomposition-product of atropine. A number of attempts have been made to synthesize such alcamines in order that by comparison we might attain a fuller knowledge of the natural alkaloids. In most cases, however, only isomeric derivatives have been obtained. These attempts have, nevertheless, afforded some very interesting contributions to the chemistry of the alkaloids, consequently they are worthy of consideration.

[68] Ahrens, B. 29, 2996.

Two processes have thus far been employed to obtain the pyridine âlcamines.

The first depends upon the condensation of aldehydes with homologues of pyridine. The reaction takes place, however, only in the case of the α-substituted products, and generally in such a way as to give rise to an unsaturated compound, the oxygen of the aldehyde being eliminated with two hydrogen atoms from the side-chain of the pyridine derivative. In this way α-picoline and acetaldehyde form α-allylpyridine:

$$\underset{\alpha\text{-Picoline}}{C_5H_4N—CH_3} + \underset{\text{Acetaldehyde}}{OCHCH_3} \rightarrow \underset{\alpha\text{-Allylpyridine}}{C_5H_4N—CH{:}CH—CH_3} + H_2O.$$

This reaction, however, takes place really in two successive stages. In the first there is a simple addition of the two molecules to form an alcamine:

$$\underset{\alpha\text{-Picoline}}{C_5H_4N—CH_3} + \underset{\text{Acetaldehyde}}{OCHCH_3} \rightarrow \underset{\alpha\text{-Picolyl methyl alcamine}}{C_5H_4N—CH_2—CHOH—CH_3}.$$

But this substance, being unstable, loses a molecule of water and is converted into the unsaturated derivative:

$$C_5H_4N—CH_2—CHOH—CH_3 \rightarrow C_5H_4N—CH{=}CH—CH_3 + H_2O.$$

By using certain precautions Ladenburg succeeded in arresting this reaction in its first phase. He accomplished this by effecting the condensation of the aldehyde with the base in the presence of water and at a temperature of 150–170°.

The second process which has been employed in preparing the alcamines is the reduction of the corresponding ketones by means of sodium amalgam:[60]

$$\underset{\text{Propionylpyridine}}{C_5H_4N—CO—C_2H_5} + 2H \rightarrow \underset{\text{Pyridyl ethyl alcamine}}{C_5H_4N—CHOH—C_2H_5}.$$

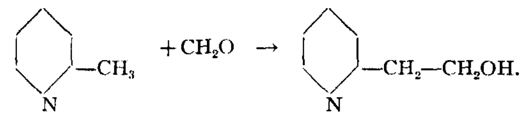
The alcamines of pyridine are in part solids, in part liquids, which, in general, can be distilled without decomposition only

[60] Engler, B. 24, 2530, 2536; 27, 1775.

under diminished pressure. They are soluble in water and in alcohol, insoluble or little soluble in ether. Under the influence of heat or dehydrating agents they readily lose a molecule of water. Treated in alcoholic solution with sodium, they add hydrogen and are converted into alcamines of piperidine.

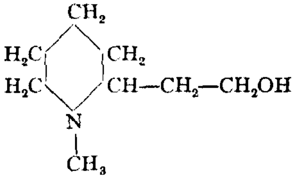
Of the many alcamines which have been prepared we will mention only those which bear an isomeric relation to some of the natural alkaloids.

1. **α-Picolyl Alcamine,** C_7H_9NO.—This body was obtained by Ladenburg[70] by the condensation of α-picoline with formaldehyde:



α-Picoline Formaldehyde α-Picolyl alcamine

It forms a non-crystallizing, sirupy liquid which boils at 179° under a pressure of 25 mm. On reduction with sodium and alcohol, it is converted into α-pipecolyl alcamine (melting-point 31–32°, boiling-point 234°.5). As a secondary base this latter reacts with potassium methyl sulphate, the imide hydrogen being exchanged for the methyl group. There is thus formed *n*-methyl pipecolyl alcamine:



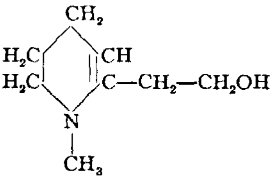
a liquid boiling at 225–226°.

The relation which this last substance bears to tropine, $C_8H_{15}NO$, a saponification-product of atropine, gives it particular interest. In composition it differs from tropine only by the addition of two hydrogen atoms, and in its chemical and

[70] Ladenburg, B. **22**, 2583; **24**, 1619; **26**, 1060.

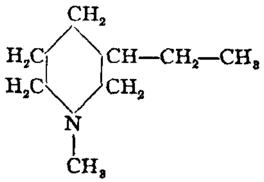
physiological behavior it so closely resembles this alkaloid that Ladenburg was led to name it *hydrotropine*. All attempts to convert it into tropine, however, proved fruitless. When it is gently oxidized with potassium ferricyanide or hydrogen peroxide, hydrotropine loses two atoms of hydrogen and there are formed two isomeric bases, *paratropine* and *α-tropine*,[71] which bear the same empirical formula ($C_8H_{15}NO$) as tropine.

2. ***n*-Methyl *α*-Pipecoline *β*-Alcamine.**—Another alcamine isomeric with atropine has been synthesized by Lipp [72] from the condensation of formaldehyde with *n*-methyltetrahydro-*α*-picoline. Lipp assigned to the base which he obtained the following constitution:



This tetrahydro-alcamine can be reduced to the hexahydro-derivative, and the latter by elimination of one molecule of water is converted into a substance which Lipp considered to be a *n-methylvinylpiperidine*.

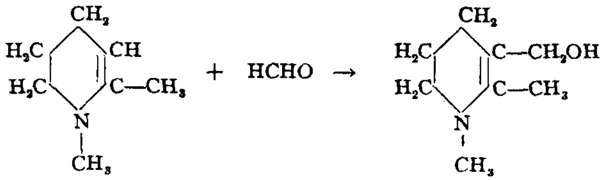
From the investigations of Ladenburg [73] it appears that Lipp's base is to be regarded as a *β*- and not an *α*-alcamine. Ladenburg found that when reduced it yields *n-methyl-β-ethyl-piperidine:*



[71] Ladenburg, B. **22**, 2583; **23**, 2709.
[72] Lipp, B. **25**, 2190, 2197; **31**, 589; A. **289**, 173; **294**, 135.
[73] Ladenburg, B. **31**, 286; A. **301**, 117.

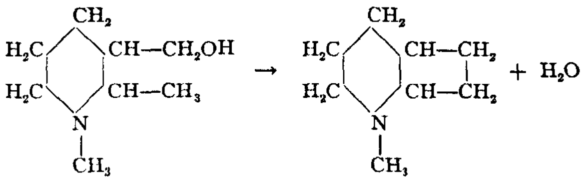
Distilled over zinc-dust, this derivative of piperidine gave *β-ethylpyridine*, whose constitution was further confirmed by its oxidation to nicotinic acid.

Ladenburg consequently formulates Lipp's reaction as follows:



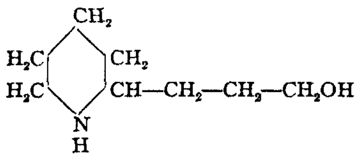
n-Methyl-α-pipecoleine — *n*-Methyl α-pipecoleine β-alcamine

Reduction converts the pipecoleine into the corresponding pipecoline which, when water is eliminated, is regarded as forming not a vinyl- but an ethylene-piperidine:



n-Methyl α-pipecoline β-alcamine — *n*-Methyl-αβ-ethylene-piperidine

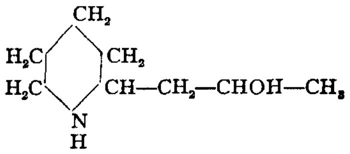
3. **α-Lutidyl Alcamine.**—This derivative was prepared by Ladenburg and Adam[74] by heating α-ethylpyridine with an aqueous solution of formaldehyde to 160°. It is a liquid which boils at 138–141° under a pressure of 17 mm. By reduction it is converted into *α-lupetidyl alcamine* (boiling-point 232–234°):



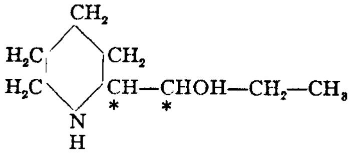
4. **α-Picolyl Methyl Alcamine.**—This was obtained by Laden-

[74] Ladenburg and Adam, B. 24, 1671.

burg[75] from the condensation of acetaldehyde with α-picoline. It crystallizes in prisms melting at 32°. On reduction it forms *α-pipecolyl methyl alcamine* (melting-point 45–47°):



5. α-**Ethyl Pyridyl Alcamine.**—This alkine results from the reduction of α-propionylpyridine,[76] which is prepared by distilling a mixture of the calcium salts of picolinic and propionic acids. It boils at 213–218° under atmospheric pressure. On reduction with sodium, the alcamine is converted into two stereoisomeric *ethyl piperidyl alcamines.* One of these melts at 99–100°; the other at 70–71°:



[75] Ladenburg, B. **22**, 2583; **23**, 2709.
[76] Engler and Bauer, B. **24**, 2530; **27**, 1775.

CHAPTER III.

CARBOXYLIC ACIDS OF PYRIDINE.

THE carboxylic acids of pyridine are derived from that base by introducing the carboxyl group, —COOH, in place of one or more atoms of hydrogen. All the acids here theoretically possible are known and their constitution has been definitely determined. They are formed in general by the oxidation of pyridine derivatives which possess a side-chain or side-chains A knowledge of their constitution is consequently of the highest importance in the chemistry of the alkaloids, since it enables us to determine the number and the position of these side-chains, as we have already seen in the preceding chapter.

These acids are solids, exhibiting at the same time an acid and a basic character. With an increase in the number of carboxyl radicals, the basicity naturally decreases. On distillation with lime they are all decomposed into pyridine and carbon dioxide. This decomposition is brought about in some cases by the action of heat alone. Polycarboxylic acids, heated above their melting-point, are generally converted into monocarboxylic acids. Under these conditions it is usually the carboxyl in the α-position that is eliminated first.

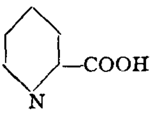
As a further distinction from the other carboxylic acids of pyridine, the α-derivatives give a color-reaction with ferrous sulphate.

A. THE MONOCARBOXYLIC ACIDS OF PYRIDINE, $C_6H_5NO_2$—$C_5H_4N(COOH)$.

Theoretically there are three monocarboxylic acids of pyridine; all of these are known. They may be formed either by

oxidizing a pyridine derivative having one side-chain, or by heating a polycarboxylic acid.

1. **Picolinic acid** (α-pyridine carboxylic acid):



Picolinic acid may be formed:

1. By oxidizing many of the α-substitution derivatives of pyridine.

2. By the action of boiling acetic acid on dipicolinic acid (page 65).[1]

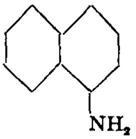
3. From the treatment of dichlorpicolinic acid with hydriodic acid; dichlorpicolinic acid results from the action of phosphorus pentachloride on comenamic acid (page 21).[2]

Picolinic acid crystallizes in prismatic needles, which melt at 137°; it is easily soluble in water and alcohol, almost insoluble in ether; with ferrous sulphate it gives a yellow coloration, and with copper acetate a violet precipitate.

When the acid is heated with lime or alcoholic potash it is decomposed into pyridine and carbon dioxide.

The position of the carboxyl in picolinic acid was definitely determined by Skraup and Cobenzl[3] in the following way:

α-Naphthylamine,



on condensation with glycerine according to the general process

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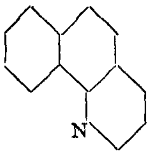
[1] Hantzsch, B. **18**, 1744.

[2] Ost, J. pr. **27**, 257.

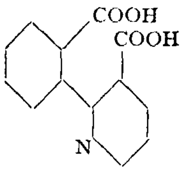
[3] Skraup and Cobenzl, M. **4**, 436.

of Skraup (see page 82), yields α-naphthoquinoline,

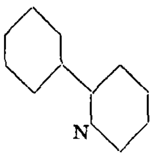


whose constitution is established by its mode of formation.

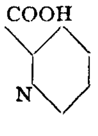
When α-naphthoquinoline is oxidized it is converted by rupture of the inner ring into α-phenylpyridine dicarboxylic acid:



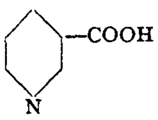
On distillation of this acid with lime, carbon dioxide is eliminated and there is formed a phenylpyridine in which the phenyl group must occupy the α-position:



From this phenylpyridine by energetic oxidation, picolinic acid is obtained, whence the acid must needs be an α-derivative of pyridine:



2. **Nicotinic acid** (β-pyridine carboxylic acid):



Modes of formation:

a. By the oxidation of nicotine.[4]

b. By the oxidation of pilocarpine.[5]

c. By the oxidation of hydrastine.[6]

d. By the oxidation of berberine.[7]

e. By the oxidation of a large number of artificial pyridine derivatives.

f. By the action of hydrochloric acid on trigonelline.[8]

g. By fusion of β-pyridine sulphonic acid with potassium cyanide and saponification of the nitrile thus formed.[9]

h. From oxynicotinic acid by treating it successively with phosphorus oxychloride and hydriodic acid. The oxynicotinic acid is formed by the action of ammonia on coumalic acid (page 21).[10]

i. By the action of heat on the following di- and tri-carboxylic acids: quinolinic acid, cinchomeronic acid, isocinchomeronic acid, dinicotinic acid, and berberonic acid (see page 61 et seq.).

The constitution of nicotinic acid is shown from its formation when quinolinic acid is heated.[11] Since the latter is an αβ-carboxyl derivative of pyridine, the acid which is obtained by the elimination of one molecule of carbon dioxide must have its carboxyl group either in the α- or β-position. But, as has been indicated, the α-derivative is picolinic acid, consequently the isomer, nicotinic acid, must be the β-acid.

The constitution of nicotinic acid may also be derived from that of β-naphthoquinoline by a series of reactions analogous to those employed in determining the constitution of picolinic acid.[12]

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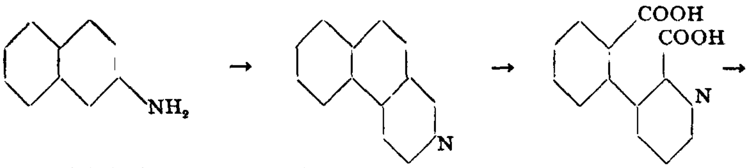
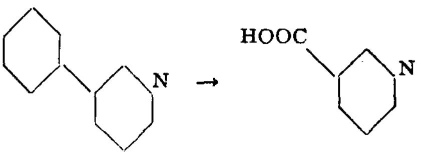
[4] Huber, A. **141**, 277. Weidel, A. **165**, 330. Laiblin, A. **196**, 134.
[5] Hardy and Calmels, C. r. **102**, 1562.
[6] Schmidt and Wilhelm, A. Pharm. **226**, 329.
[7] Schilbach, J. 1886, 1722.
[8] Jahns, B. **20**, 2840.
[9] O. Fischer, B. **15**, 63.
[10] von Pechmann and Welsh, B. **17**, 2384.
[11] Hoogewerff and van Dorp, R. **1**, 1, 107.
[12] Skraup and Vortmann, M. **4**, 569.



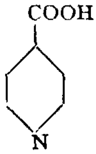
β-Naphthylamine β-Naphthoquinoline β-Phenylpyridine dicarboxylic acid



β-Phenylpyridine Nicotinic acid

Nicotinic acid crystallizes in needles (melting-point 229°) which are insoluble in ether, little soluble in cold water, but readily soluble in alcohol and in boiling water. Its solution on the addition of copper acetate gives a light-blue precipitate of the copper salt.

3. **Isonicotinic acid** (γ-pyridine carboxylic acid):



Modes of formation:

a. By the oxidation of a large number of γ-derivatives of pyridine.

b. By the partial decomposition of a number of di-and tri-carboxylic acids: lutidinic acid, cinchomeronic acid, carbocinchomeronic acid, carbolutidinic acid, and berberonic acid (page 61 et seq.).

c. By the successive action of phosphorus pentachloride and hydriodic acid on citrazinic acid, $C_5H_2(OH)_2NCOOH$ (see page 157).[13]

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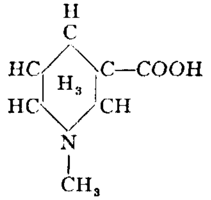
[13] Behrmann and Hofmann, B. 17, 2681.

Isonicotinic acid forms needles which melt at 306°; it is very difficultly soluble in water, alcohol, and ether; its copper salt is green.

The position of the carboxyl group in isonicotinic acid is shown indirectly. The proof in general depends upon the exclusion of the other possibilities. In picolinic and nicotinic acids the carboxyl occupies respectively the α- and β-positions, consequently the third form theoretically possible must have the carboxyl in the γ-position.

Hydrated Monocarboxylic Acids of Pyridine.—Like pyridine itself, the carboxylic acids of pyridine readily add hydrogen. As yet, however, no dihydro-derivative has been prepared.

Of the *tetra*hydro-derivatives, we may mention here *n-methyl-tetrahydronicotinic acid:*



Jahns[14] obtained this acid together with the hexahydro-derivative by the reduction of nicotinic acid methyl chloride with tin and hydrochloric acid. The body is identical with a natural alkaloid, ***arecaïdine*** (see p. 152).

The three theoretically possible hexahydro-pyridine mono-carboxylic acids, or *piperidine monocarboxylic acids*, are formed by the reduction of the three pyridine monocarboxylic acids with sodium and alcohol.[15] They are well-crystallized bodies, easily soluble in water; they possess partly a basic, partly an acid character; with nitrous acid they form, like other secondary bases, nitrosamines:

α-Piperidine carboxylic acid, or ***pipecolinic acid,*** melting-point 258°.

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[14] Jahns, A. Pharm. **229**, 669.
[15] Ladenburg, B. **24**, 640; **25**, 2768.

β-Piperidine carboxylic acid, or *nipecotinic acid*, melting-point 249–250°.

γ-Piperidine carboxylic acid, or *isonipecotinic acid*, melting-point above 320°.

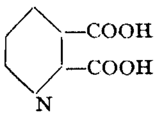
B. The Dicarboxylic Acids of Pyridine, $C_7H_5NO_4—C_5H_3N(COOH)_2$.

The six pyridine dicarboxylic acids theoretically possible are all known. They are formed in general by the oxidation of pyridine derivatives having two side-chains.

Distilled with lime, they are converted into pyridine; heated alone, they ordinarily lose one molecule of carbon dioxide and yield monocarboxylic acids.

For a long time the constitution of these acids was hidden in obscurity; to-day this question may be regarded as solved, thanks to the work of Hantzsch and his students.

1. **Quinolinic acid** (αβ-pyridine dicarboxylic acid):

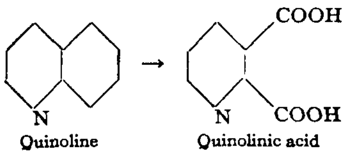


This acid crystallizes in anhydrous prisms which melt with decomposition at 192° and are thereby converted into nicotinic acid. It is little soluble in water, alcohol, and ether; its aqueous solution is colored orange by iron sulphate.

The acid is formed by the oxidation of quinoline itself,[16] or of quinoline derivatives in which the side-chains are attached to the benzol nucleus. It is most advantageously prepared by the oxidation of alizarin-indigo-blue with nitric acid.

[16] Hoogewerff and van Dorp, R. 1, 1, 107; B. 12, 747; A. 204, 117.

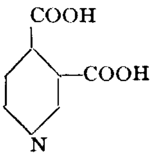
The position of the carboxyl groups in quinolinic acid follows directly from its formation from quinoline (see p. 79):



This acid is then the direct analogue in the pyridine series of phthalic acid in the benzol series. When heated, however, it does not form an anhydride, but, owing to the instability of the α-carboxyl, is decomposed into carbon dioxide and nicotinic acid.

The anhydride of quinolinic acid may nevertheless be obtained by treating the acid with acetic anhydride.[17] It forms prisms melting at 134°.5 and shows all the reactions characteristic of phthalic anhydride (formation of fluoresceïn, condensation with aromatic hydrocarbons in the presence of aluminum chloride, etc.).

2. **Cinchomeronic acid** (βγ-pyridine dicarboxylic acid):



Cinchomeronic acid is obtained quite frequently as a decomposition-product of various cinchona alkaloids; from the action of nitric acid on quinine, cinchonidine, cinchonine, and apoquinine;[18] from the oxidation of cinchoninic acid, which is derived from cinchonine by the action of chromic acid;[19] and from the oxidation of β-collidine, which can be prepared from meroquinene.[20]

Other sources from which cinchomeronic acid may be obtained are:

[17] Bernthsen and Mettegang, B. 20, 1208.
[18] Weidel, A. 173, 96; B. 12, 1146. Königs, B. 30, 1326.
[19] Skraup, B. 12, 1107.
[20] Königs, B. 27, 1501. Oechsner, Bl. 42, 100; 43, 106.

a. The oxidation of lepidine.[21]

b. The oxidation of isoquinoline and of dimethoxyisoquinoline.[22]

c. The action of hydrochloric acid on apophyllenic acid, an oxidation product of cotarnine.[23]

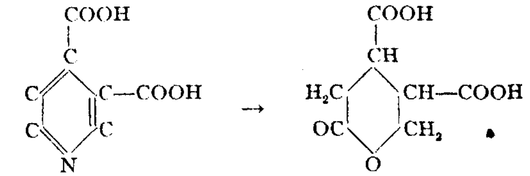
d. The decomposition by heat of α-carbocinchomeronic acid, of β-carbocinchomeronic acid, and of berberonic acid (page 67 et seq.).

Cinchomeronic acid crystallizes in prisms, little soluble in water, insoluble in ether. The aqueous solution is not colored red by ferrous sulphate.

The crystals melt with decomposition at 258–259°; the residue contains a mixture of nicotinic and isonicotinic acids. This shows that the two carboxyls in cinchomeronic acid occupy the same positions as those in nicotinic and isonicotinic acids, viz., the β- and γ-positions.

Cinchomeronic acid like quinolinic acid is accordingly an *ortho*-pyridine dicarboxylic acid and forms an anhydride when it is heated with acetic anhydride.[24] This anhydride crystallizes in plates which melt at 77–78°. Like its isomer, it gives the same general reactions as phthalic anhydride.

While the pyridine ring is in general quite stable, Weidel[25] succeeded by a very simple reaction in eliminating the nitrogen atom in cinchomeronic acid. When the acid is treated with sodium amalgam it is converted into cinchonic acid:



Cinchomeronic acid — Cinchonic acid

[21] Hoogewerff and van Dorp, R. 2, 1.

[22] Hoogewerff and van Dorp, R. 4, 285.

[23] Vongerichten, B. 13, 1635; A. 210, 79.

[24] Goldschmidt and Strache, M. 10, 156.

[25] Weidel, B. 12, 1146; M. 13, 578.

The sixth and last pyridine dicarboxylic acid is formed by the oxidation of a lutidine in coal-tar,[30] of α-collidine,[31] and of some other $\alpha\alpha'$-derivatives. It occurs in needles which contain 1–1½ molecules of water of crystallization and which when dried melt with decomposition at 236°. It is little soluble in water, alcohol, and ether, and is colored red by the addition of ferrous sulphate.

The constitutions of the five preceding acids having been established, there remains for dipicolinic acid only one possible position for the two carboxyl groups, viz., the $\alpha\alpha'$. This indirect proof is further supported by the fact that, when the acid is heated, pyridine is formed immediately without the intermediate separation of a monocarboxylic acid, as in the case of the other dicarboxylic acids of pyridine.

It may be noted furthermore that Hantzsch[32] by the action of acetic acid on dipicolinic acid has obtained picolinic acid in small quantities.

C. THE TRICARBOXYLIC ACIDS OF PYRIDINE,

$$C_8H_5NO_6—C_5H_2N(COOH)_3.$$

According to theory there should be six isomeric pyridine tricarboxylic acids; all these are known. Their constitution has been established as in the case of the dicarboxylic acids by the work of Hantzsch and his students. Of these acids two, α-carbocinchomeronic acid and berberonic acid, result as oxidation-products of natural alkaloids; the others have been synthesized.

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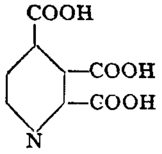
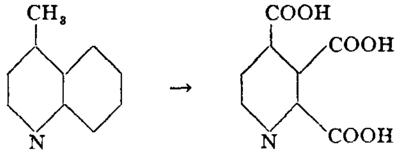
[30] Lunge and Rosenberg, B. **20**, 127.
[31] Oechsner, Bl. **42**, 100. Schultz, B. **20**, 2720.
[32] Hantzsch, B. **18**, 1744.

1. **α-Carbocinchomeronic acid** (αβγ-pyridine tricarboxylic acid):



This acid was first obtained in 1874 by oxidizing cinchonine with nitric acid.[33] Later it was prepared by the oxidation of several other cinchona alkaloids (quinine, quinidine, cinchonidine)[34] and their derivatives, cinchoninic and quininic acids.[35] It is also formed by the action of potassium permanganate on papaverine [36] and on lepidine.[37]

The last method of formation establishes the position of the carboxyl groups in α-carbocinchomeronic acid. Since lepidine is γ-methylquinoline, the acid resulting from its oxidation must be αβγ-pyridine tricarboxylic acid:

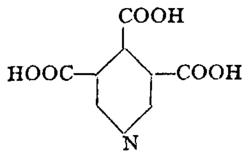


Lepidine α-Carbocinchomeronic acid

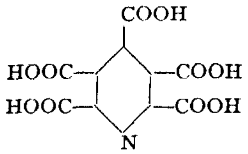
α-Carbocinchomeronic acid crystallizes in plates with 1½ molecules of water. The anhydrous acid melts at 249–250° and is at the same time converted into cinchomeronic acid by loss of the α-carboxyl group.

[33] Weidel, A. **173**, 101; B. **12**, 415.
[34] Hoogewerff and van Dorp, A. **204**, 84; B. **12**, 158, 1287; **13**, 152. Ramsay and Dobbie, Soc. **35**, 189.
[35] Skraup, M. **1**, 184; **2**, 600; A. **201**, 308.
[36] Goldschmiedt, M. **6**, 372, 954.
[37] Hoogewerff and van Dorp, B. **13**, 1640.

2. **β-Carbocinchomeronic acid** (βγβ'-pyridine tricarboxylic acid):



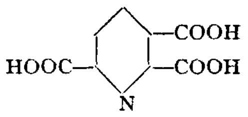
Weber[38] prepared this acid by heating to 220° the di-potassium salt of pyridine pentacarboxylic acid:



The two molecules of carbon dioxide which are thus eliminated come undoubtedly from the carboxyls which occupy the αα'-positions. From this it follows that the acid is a βγβ'-derivative of pyridine.

Carbocinchomeronic acid crystallizes in leaflets with three molecules of water. It is little soluble in cold water; the anhydrous acid melts at 261° with decomposition into cinchomeronic acid.

3. **Carboisocinchomeronic acid** (αβα'-pyridine tricarboxylic acid):

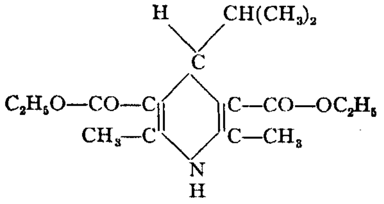


This isomer is obtained by oxidizing αα'-dimethylnicotinic acid with potassium permanganate.[39]

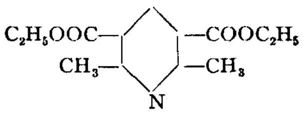
αα'-Dimethylnicotinic acid is synthesized in the following way:

[38] Weber, A. 241, 1.
[39] Weiss, B. 19, 1305.

By the condensation of aceto-acetic ester with isobutyraldehyde and ammonia there is formed, in accordance with the synthesis of Hantzsch (see p. 45), the ester of ***hydroisopropyl-lutidine dicarboxylic acid:***

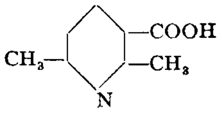


This substance, which is a derivative of dihydropyridine, loses by the oxidizing action of nitrous acid, both additional hydrogen atoms and the isopropyl group in the γ-position and there is formed an ester of *lutidine dicarboxylic acid:*



This ester can be saponified to the free lutidine dicarboxylic acid, which loses carbon dioxide when heated.

The monobasic acid obtained by this treatment must consequently have the following constitution:



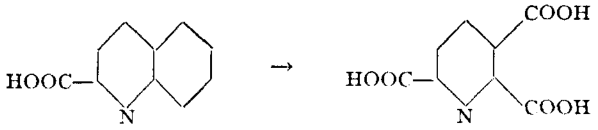
$\alpha\alpha'$-Dimethylnicotinic acid

As we have seen, this $\alpha\alpha'$-dimethylnicotinic acid is oxidized by the action of potassium permanganate to carboisocinchomeronic acid, which must accordingly be *$\alpha\beta\alpha'$-pyridine tricarboxylic acid.*

In another way von Miller[40] reached the same conclusion

[40] von Miller, B. 24, 1900.

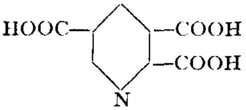
regarding the constitution of carboisocinchomeronic acid. He obtained the acid by oxidizing quinaldic acid with potassium permanganate:



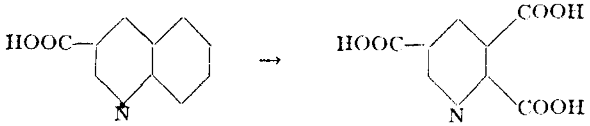
Quinaldic acid Carboisocinchomeronic acid

Carboisocinchomeronic acid forms small leaflets, which contain two molecules of water of crystallization. Of all the tricarboxylic acids of pyridine it is the only one easily soluble in water; in alcohol and ether it is almost insoluble. It shows no definite melting-point, since when heated it gradually undergoes decomposition with the elimination of carbon dioxide.

4. **Carbodinicotinic acid** ($\alpha\beta\beta'$-pyridine tricarboxylic acid),



is formed by the oxidation of β-quinoline carboxylic acid with potassium permanganate.[41] Its constitution follows from its mode of formation:



β-Quinoline carboxylic acid Carbodinicotinic acid

It has also been obtained by oxidation from α-picoline-$\beta\beta'$-dicarboxylic acid,[42] and from $\alpha\beta\beta'$-dimethylethylpyridine.[43]

The acid crystallizes in needles with two molecules of water; it is somewhat difficultly soluble in water and alcohol. It possesses

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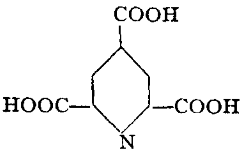
[41] Riedel, B. **16**, 1609.
[42] Weber, A. **241**, 1.
[43] Dürkopf and Schlangk, B. **21**, 832, 2707.

no definite melting-point, but when heated above 150° is slowly decomposed into dinicotinic acid.

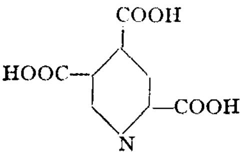
5. Carbolutidinic acid ($\alpha\gamma\alpha'$-pyridine tricarboxylic acid),



results as an oxidation-product of symmetrical trimethylpyridine (p. 45).[44] This reaction naturally establishes the constitution of the acid. It is further obtained by the oxidation of uvitonic acid (p. 33) with potassium permanganate.[45]

Carbolutidinic acid forms needle-like crystals containing two molecules of water. The acid is little soluble in water, alcohol, and ether. In the anhydrous condition it melts at 227° with decomposition into isonicotinic acid.

6. Berberonic acid ($\alpha\gamma\beta'$-pyridine tricarboxylic acid):



This acid is formed as the chief product of the oxidation of berberine by means of nitric acid.[46] It has also been prepared by oxidizing one of the trimethylpyridines from coal-tar. Its constitution must be represented by the above formula, since the constitutions of its five possible isomers have already been determined. In full accord with this formula is also its general behavior. Boiled with glacial acetic acid it loses carbon

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[44] Voigt, A. **228**, 29.
[45] Böttinger, B. **13**, 2048; A. **229**, 248.
[46] Weidel, B. **12**, 410. Fürth, M. **2**, 416.

dioxide and is converted into cinchomeronic acid; at its melting-point (243°) it decomposes into a mixture of nicotinic and isonicotinic acids; the α-position of a carboxyl group is indicated by its giving a red coloration with ferrous sulphate.

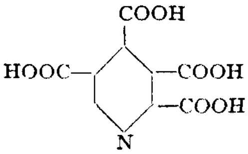
Berberonic acid crystallizes in prisms which contain two molecules of water and which are little soluble in alcohol and water.

D. Pyridine Petracarboxylic Acids,

$$C_9H_5NO_8—C_5HN(COOH)_4.$$

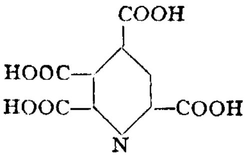
All three tetracarboxylic acids of pyridine are known and their constitution has been established. They have not as yet been derived from the natural alkaloids, but are obtained as oxidation-products of synthesized derivatives of pyridine.

1. **$\alpha\beta'$-Dicarbocinchomeronic acid** ($\alpha\beta\gamma\beta'$-pyridine tetracarboxylic acid),



is prepared by the oxidation of *$\alpha\gamma$-dimethyldinicotinic acid.*[47] It forms transparent prisms containing water of crystallization, and on being heated to 160° is decomposed into β-carbocinchomeronic acid.

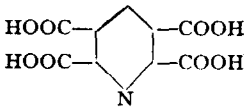
2. **Unsymmetrical tetracarboxylic acid** ($\alpha\gamma\beta'\alpha'$-pyridine tetracarboxylic acid),



[47] Weber, A. 241, 1.

is formed by oxidizing the potassium salt of $\alpha\gamma\alpha'$-trimethylnicotinic acid,[48] also by oxidizing flavenol, an artificial derivative of quinoline.[49] It crystallizes in fine needles with two molecules of water; the anhydrous acids melt at 227°.

3. $\alpha\alpha'$-**Dicarbodinicotinic acid** ($\alpha\beta\beta'\alpha'$-pyridine tetracarboxylic acid):



This acid is obtained from $\alpha\alpha'$-dimethyldinicotinic acid by treatment with potassium permanganate.[50] It crystallizes with two molecules of water in glittering needles which when heated are converted into dinicotinic acid.

E. Pyridine Pentacarboxylic Acid,

$$C_{10}H_5NO_2—C_5N(COOH)_5.$$

The one acid of this formula capable of existence is prepared by oxidizing with potassium permanganate the potassium salt of collidine dicarboxylic acid.[51] It crystallizes with varying quantities of water in microscopic needles which on being heated decompose into carbon dioxide and β-carbocinchomeronic acid.

Betaïnes of the Acids in the Pyridine Series.

The acids of pyridine yield derivatives whose constitution is of the same nature as that of betaïne. As is known, betaïne, which occurs in sugar-beets and other plants (see Betaïne), is the inner

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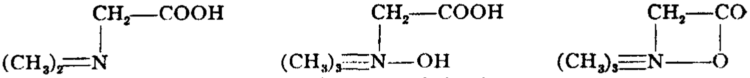
[48] Michael, A. 225, 121.
[49] Fischer, B. 19, 1036.
[50] Hantzsch and Weiss, B. 19, 284.
[51] Hantzsch, A. 215, 62.

anhydride of the methyl hydroxide derivative of dimethylamido-acetic acid:



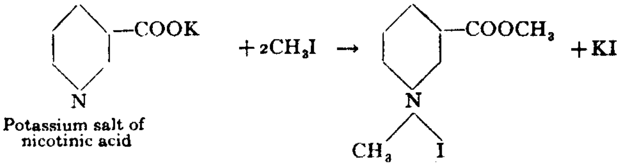
Dimethylamido-acetic acid — Methyl hydroxide of dimethyl-amido-acetic acid — Betaïne

The carboxylic acids of pyridine behave in the same way as dimethylamido-acetic acid. Their alkyl hydroxides are unstable and are converted spontaneously, by loss of one molecule of water, into *betaïnes:*

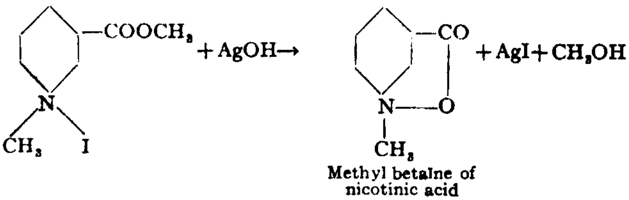
Methyl hydroxide of pyridine monocarboxylic acids — Methyl betaïne of pyridine monocarboxylic acids

Hantzsch[52] prepared the betaïnes of nicotinic, picolinic, and collidine carboxylic acids by heating the potassium salt of these acids with methyl iodide and subsequently treating the addition-product with silver oxide.

With nicotinic acid, for example, the reaction is as follows:



Potassium salt of nicotinic acid — Methyl iodide of nicotinic acid methyl ester

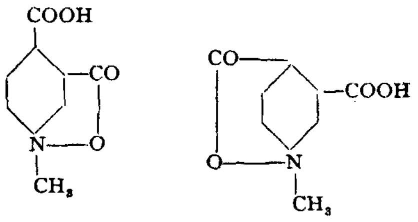


Methyl betaïne of nicotinic acid

[52] Hantzsch, B. 19, 31.

This betaïne is obtained more simply by the direct treatment of nicotinic acid methiodide with silver oxide.[53]

Roser[54] secured the methyl betaïne of cinchomeronic acid by heating this acid with methyl iodide to 100°. Its constitution must be represented by one of the two following formulæ:



The betaïnes of the pyridine acids invite particular attention because of their close relation to some of the natural alkaloids. The methyl betaïne of nicotinic acid is shown to be identical with *trigonelline* (see page 149).[55]

The methyl betaïne of cinchomeronic acid, on the other hand, has been identified with *apophyllenic acid*, which Wöhler obtained by the oxidation of cotarnine (page 298) and which is also formed, according to Freund, from hydrastinine (page 317).

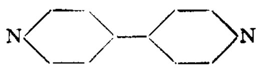
[53] Pictet and Süssdorff, *unpublished investigation.*
[54] Roser, A. 234, 116.
[55] Jahns, B. 20, 2840.

CHAPTER IV.

DIPYRIDYLS, $C_{10}H_8N_2$—(C_5H_4N—C_5H_4N).

THE dipyridyls bear the same relation to pyridine that diphenyl bears to benzol. They are to be considered as resulting from the union of two molecules of pyridine with the elimination of a hydrogen atom from each molecule. According to the point of juncture, there are theoretically possible six isomeric dipyridyls ($\alpha\alpha$, $\beta\beta$, $\gamma\gamma$, $\alpha\beta$, $\alpha\gamma$, $\beta\gamma$). Of these but four are as yet well known.

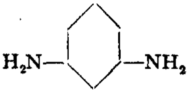
The first dipyridyl was obtained in 1870 by Anderson[1] and later by Weidel and Russo[2] by the action of sodium on pyridine at the ordinary temperature. On oxidation this dipyridyl is converted into isonicotinic acid; it is consequently *$\gamma\gamma$-dipyridyl:*



It crystallizes from hot water in needles melting at 111–112°; it boils without decomposition at 305°.

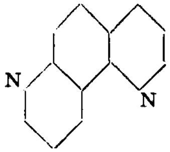
The constitution of two other dipyridyls, prepared by Skraup and Vortmann,[3] follows directly from their synthesis. From phenylene diamine there is formed, by the quinoline synthesis of Skraup (page 82), the so-called *phenanthroline:*

[1] Anderson, A. **154**, 270.
[2] Weidel and Russo, M. **3**, 851.
[3] Skraup and Vortmann, M. **3**, 599; **4**, 591.

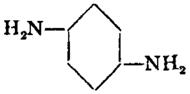


m-Phenylene diamine

↓

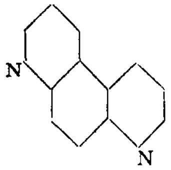


Phenanthroline



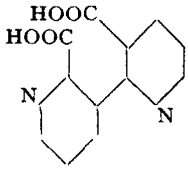
p-Phenylene diamine

↓

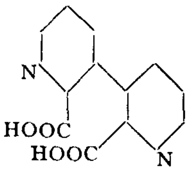


Pseudo-phenanthroline

On oxidation these two bases are converted into the following acids:

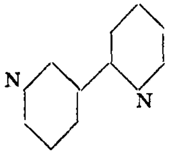


αβ-Dipyridyl dicarboxylic acid

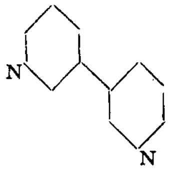


ββ-Dipyridyl dicarboxylic acid

Subjected to distillation, the calcium salts of these acids are decomposed, with elimination of carbon dioxide, into *αβ*- and *ββ*-dipyridyl respectively:



αβ Dipyridyl



ββ-Dipyridyl

αβ-Dipyridyl is a liquid boiling at 296° (uncorrected 287°); it is converted by oxidation into nicotinic acid.

ββ-Dipyridyl is a solid which melts at 68° and boils at 296° (uncorrected 287°); on oxidation it also yields nicotinic acid.

A fourth isomeric dipyridyl was obtained by Blau[4] on dis-

[4] Blau, M. **10**, 375; **13**, 330; B. **24**, 326.

tilling the copper salt of picolinic acid. It melts at 69°.5 and boils at 272°.5. Oxidation converts it into picolinic acid; it is consequently *αα-dipyridyl.*

Roth [5] obtained a dipyridyl by leading the vapor of pyridine through a red-hot tube; it is a liquid boiling at 280–282°. Whether this is a fifth isomer, or is identical with one of the four dipyridyls already noted, has not been determined.

The dipyridyls readily add hydrogen and thereby form according to the conditions of the experiment two kinds of derivatives. On being reduced with tin and hydrochloric acid only one-half the molecule is affected and there is formed a *pyridylpiperidine;* by the stronger reducing action of sodium and alcohol both the pyridine rings are attacked and there results a *dipiperidyl.*

Of the pyridylpiperidines, $C_5H_4N{-}C_5H_{10}N$, only those from *ββ-* and *γγ*-dipyridyl have been prepared. These derivatives are isomeric with nicotine and in their physical and physiological behavior show a close resemblance to this alkaloid.

ββ-Pyridylpiperidine (*nicotidine*) is a liquid boiling at 287–289°, quite soluble in water, and very poisonous.

γγ-Pyridylpiperidine (*isonicotine*) is a solid crystallizing in needles which melt at 78°. Its boiling-point lies above 260°. It is easily soluble in water, is less poisonous than nicotine, and on oxidation forms isonicotinic acid.

The dipiperidyls, $(C_5H_{10}N)_2$, have the same composition as hexahydronicotine, but none of them is identical with this substance. This shows that nicotine is not, as was once supposed, a derivative of a dipyridyl.

αα-Dipiperidyl is a liquid boiling at 259°.

αβ-Dipiperidyl melts at 68–69° and boils at 267–268°.

γγ-Dipiperidyl forms needles which melt near 160°.

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[5] Roth, B. 19, 360.

CHAPTER V.

QUINOLINE.

In the year 1834 Runge[1] extracted from coal-tar a base of the formula C_9H_7N, which he named *leucol*, or *leucoline*. A few years later (1842) Gerhardt[2] obtained, by the distillation of cinchonine with caustic potash, a base of the same composition which he called *quinoleïne*. These substances were for a long time regarded as isomers, since they appeared to give different color reactions. It was shown later, however, that this difference was due to impurities[3] and that leucol and quinoleïne are identical.

Quinoleïne, or *quinoline*, as it is now known, is a colorless, oily liquid which solidifies at $-19^\circ.5$ and boils at 240°. Its odor reminds one of benzaldehyde or nitrobenzol. Its specific gravity at 20° is 1.0947. It is almost insoluble in water; on the other hand it is soluble in all proportions in alcohol, ether, and most organic solvents.

Quinoline is a tertiary base; in its chemical behavior it closely resembles pyridine. Körner in 1869 advanced the hypothesis that the relation between the two bases is the same as that between naphthalene and benzol and that consequently quinoline is to be considered as a naphthalene in which one of the α-CH groups is replaced by an atom of nitrogen:

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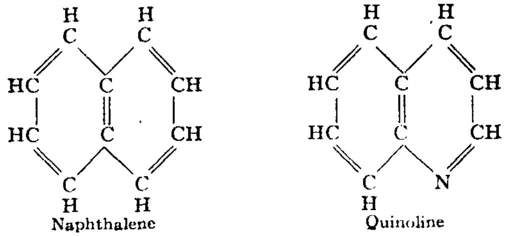
[1] Runge, *Poggendorff's Ann. der Phys. und Chem.*, **31**, 68.

[2] Gerhardt, A. **42**, 310; **44**, 279.

[3] Hofmann, A. **47**, 31; **74**, 15. Hoogewerff and van Dorp, R. **1**, 1, 107; **2**, 41. Jacobsen and Reimer, B. **16**, 513, 1082.

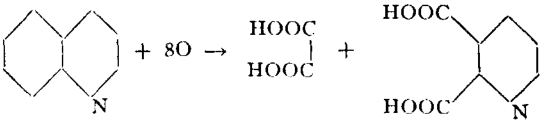


Naphthalene Quinoline

The molecule of quinoline results, then, from the union of a benzol and a pyridine ring.

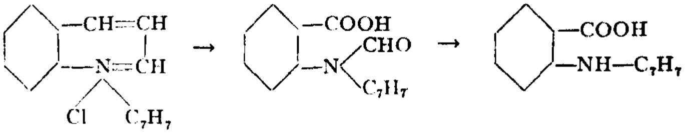
This hypothesis has been verified by all the syntheses of quinoline and by its behavior towards oxidizing agents.

Treated with potassium permanganate, quinoline yields oxalic acid and the dibasic acid, quinolinic acid (page 61). On distillation with lime the latter is converted into carbon dioxide and pyridine:



Quinoline Oxalic acid Quinolinic acid

While in the above case the pyridine ring shows the greater stability, somewhat different results are obtained when the permanganate acts not upon quinoline but upon the addition-product which the base forms with benzyl chloride. It is the pyridine ring which is now destroyed, since it is rendered less resistant by the pentavalent condition of the nitrogen atom. There is thus obtained a mixture of benzylanthranilic and formylbenzylanthranilic acids:[4]

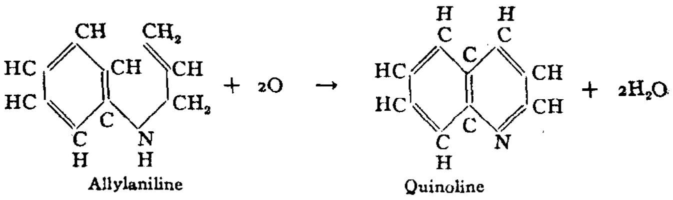


Benzyl chloride of quinoline Formylbenzylanthranilic acid Benzylanthranilic acid

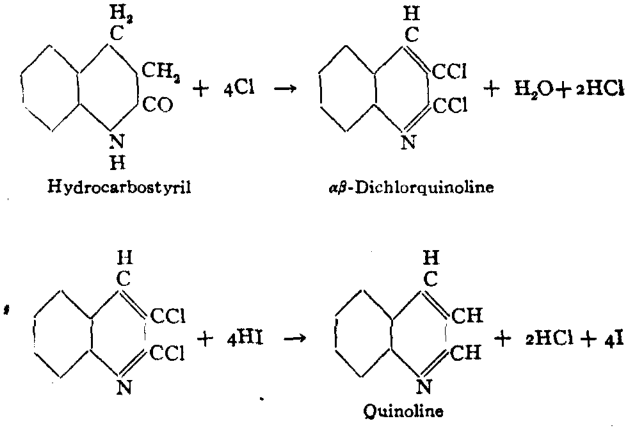
[4] Claus and Glykhen, B. 16, 1283.

Synthesis of Quinoline.—A large number of synthetic processes are known; only the more important of these, however, will be here considered.

1. The first synthesis of quinoline was made by Königs[5] in 1879 by passing the vapor of allylaniline over lead oxide heated to redness.



2. In the same year Baeyer[6] succeeded in converting hydrocarbostyril, the inner anhydride of *o*-amidohydrocinnamic acid, $C_6H_4\left<\begin{matrix}CH_2—CH_2\\NH————\end{matrix}\right>CO$, into quinoline by treating it successively with phosphorus pentachloride and hydriodic acid:



[5] Königs, B. 12, 453.
[6] Baeyer, B. 12, 460, 1320.

3. In 1880 Königs[7] obtained small quantities of quinoline by heating the condensation-product of aniline and acroleïn, so also when he heated nitrobenzol (or aniline) with glycerine and sulphuric acid at 180–190°.

This latter mode of formation, which was, indeed, incited by the work of Graebe[8] on alizarine-blue, was soon worked out by Skraup[9] as an excellent method for the synthesis of quinoline. By employing not as Königs had done, *either* aniline *or* nitrobenzol, but a mixture of *both* these substances with glycerine and sulphuric acid, he obtained a 60% yield of quinoline.

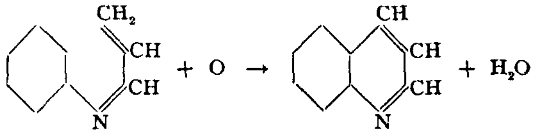
We thus have a simple and practical method for the synthesis of quinoline, nor is the method limited to the synthesis of this base, but it may be generalized and thereby extended to the preparation of many of the derivatives of quinoline.

The mechanism of the reaction of Skraup is most probably to be explained as follows: By the dehydrating action of the sulphuric acid the glycerine is converted into acroleïn; this unites with the aniline, and the condensation-product thus formed is oxidized by a part of the nitrobenzol, whereby the pyridine ring is closed.

$$\text{I. } \underset{\text{Glycerine}}{CH_2OH{-}CHOH{-}CH_2OH} \rightarrow \underset{\text{Acroleïn}}{CH_2{=}CH{-}CHO} + 2H_2O$$

$$\text{II. } \underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Acroleïn}}{OCH{-}CH{=}CH_2} \rightarrow \underset{\text{Acroleïn-aniline}}{C_6H_5N{=}CH{-}CH{=}CH_2} + H_2O$$

III.



Acroleïn-aniline Quinoline

It was first thought that the nitrobenzol shared in the formation of the benzol nucleus in quinoline; but this is not the case;

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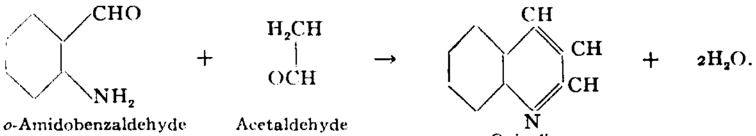
[7] Königs, B. **13**, 911.
[8] Graebe, B. **12**, 1416; A. **201**, 333.
[9] Skraup, M. **1**, 316; **2**, 141.

it acts only as an oxidizing agent. This was shown by the fact that the nitrobenzol could be replaced by nitrophenols without the formation of oxyquinolines, also by picric acid or arsenic acid.[10]

4. In 1883, Friedländer and Gohring[11] synthesized quinoline by the condensation of *o*-amidobenzaldehyde with acetaldehyde. The condensation is effected simply by the addition of a few drops of caustic soda:



o-Amidobenzaldehyde Acetaldehyde Quinoline

5. Baeyer and Drewsen[12] have prepared quinoline by the reduction of *o*-nitrocinnamic aldehyde,

$$C_6H_4\left\langle\begin{array}{l}CH{=}CH{-}CHO\\NO_2\end{array}\right.$$

6. Rügheimer[13] effected its synthesis by the action of phosphorus pentachloride on malonanilic acid, $C_6H_5NH{-}COCH_2{-}COOH$, and the reduction of the resulting chlorquinoline with hydriodic acid.

7. Another investigator[14] states that quinoline is formed by the action of glyoxal on orthotoluidine at 150°.

In general the base is obtained by the distillation of quinoline carboxylic acids over lime and by the reduction of oxyquinolines with zinc-dust.

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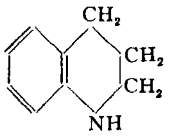
[10] Knüppel, B. 29, 703.
[11] Friedländer and Gohring, B. 15, 2572; 16, 1833.
[12] Baeyer and Drewsen, B. 16, 2207.
[13] Rügheimer, B. 17, 737; 18, 2975.
[14] Kulisch, M. 15, 276.

Addition-products of Quinoline.

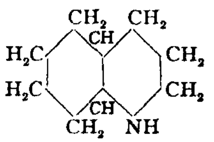
As an unsaturated compound, quinoline forms addition-products with bromine, iodine, etc. These elements add themselves easily to the pyridine ring, less readily to the benzol. Nascent hydrogen also readily acts upon quinoline. If the base is treated with reducing agents such as zinc and hydrochloric acid, sodium and alcohol, etc., four atoms of hydrogen are added and there is formed *tetrahydroquinoline*, $C_9H_{11}N$, a secondary base (boiling-point 244°):



By oxidizing agents this is reconverted into quinoline.[15]

Another tetrahydroquinoline was prepared by Oechsner[16] from the product obtained by distilling cinchonine and brucine with caustic potash. It possesses the comparatively low boiling-point of 215°. It is consequently not identical with the preceding, and the benzol ring must be regarded as the ône reduced.

By heating tetrahydroquinoline at 230° with hydriodic acid and phosphorus there have been obtained a *hexahydroquinoline* (boiling-point 226° at 720 mm.) and a *dekahydroquinoline*, which crystallizes in needles melting at 48°.5 and boils at 204°.[17]



[15] Wischnegradsky, B. **12**, 1481; **13**, 2312, 2400. Lellmann and Reusch, B. **22**, 1389.

[16] Oechsner, C. r. **94**, 87; **99**, 1077.

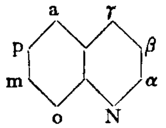
[17] Bamberger and Lengfeld, B. **23**, 1138.

Substitution-products of Quinoline.

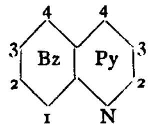
Theoretically seven isomeric monosubstitution-products are to be expected. Of the polysubstituted derivatives with like substituents there are the following possibilities:

Disubstitution-products	21	isomers
Trisubstitution-products	35	"
Tetrasubstitution-products	35	"
Pentasubstitution-products.	21	"
Hexasubstitution-products..............	7	"
Heptasubstitution-products	1	"

To designate the positions in the quinoline molecule there are generally employed for the pyridine nucleus the Greek letters α, β, γ; for the benzol nucleus the prefixes *ortho*, *meta*, *para*, and *ana*, as follows:

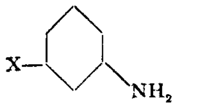


The positions in the quinoline molecule may also be designated by numbers. In this case the abbreviations *Bz* and *Py* are used to indicate the ring referred to:

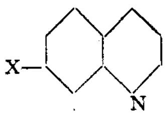


Quinolines substituted in the benzol ring can be obtained by the synthesis of Skraup; we need only replace the aniline by one of its substitution-products. The position of the substituent remains the same in the derivative of quinoline as in that of the aniline; ortho and para substituted anilines yield ortho- and para-quinolines. In the case of meta substituted

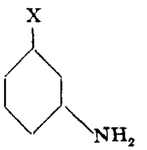
anilines, a glance at the following formulæ will show that we may here obtain both meta- and ana-derivatives:



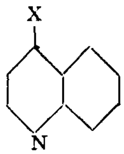
Meta substituted aniline



Meta substituted quinoline



Meta substituted aniline



Ana substituted quinoline

Ordinarily the two isomers are formed in the same reaction. Of the many substitution-products of quinoline known, the hydroxyl derivatives have attained considerable importance in the determination of the constitution of the natural alkaloids.

Oxyquinolines, $C_9H_6(OH)N$.

Of the seven monoxyquinolines theoretically possible six are known.

The four isomers which have the hydroxyl group in the benzol ring and which sometimes receive the name of *quinophenols* may be prepared from the amidophenols by the synthesis of Skraup,[18] or by fusing quinoline monosulphonic acids with potassium hydroxide,[19] or, lastly, by diazotizing the amido-quinolines.[20]

The quinophenols possess both the properties of a phenol and of a base. On oxidation they, like quinoline itself, are converted into quinolinic acid; on reduction they yield tetrahydro-quinoline.

[18] Skraup, M. 3, 536.
[19] O. Fischer, B. 14, 443, 1366; 15, 1979; 16, 450, 721. Happ, B. 17, 193.
[20] Skraup, M. 5, 532. Claus and Massau, J. pr. 48, 170.

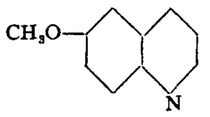
o-Oxyquinoline crystallizes in needles which melt at 75–76°; its boiling-point is 266°.

m-Oxyquinoline forms needles melting at 235-238°.

a-Oxyquinoline crystallizes either in needles or leaflets; it melts at 224°.

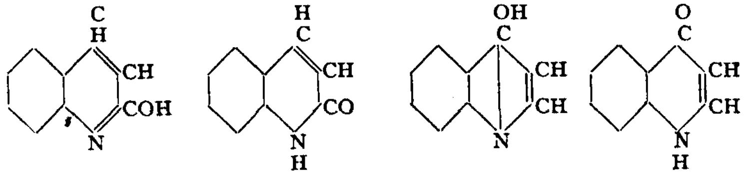
p-Oxyquinoline yields prismatic csystals; it melts at 193° and boils above 360°. This derivative is formed by heating xanthoquininic acid, a decomposition-product of quinine (p. 105).[21]

The methyl ether of *p*-oxyquinoline has been known since 1879, at which time Butlerow and Wischnegradsky,[22] by melting quinine with caustic potash, obtained an oily base of the formula $C_{10}H_9NO$ (boiling-point 304–305°), which they named *quinolidine.* In 1885 Skraup [23] showed that this base was *p-methoxyquinoline:*



This derivative may be formed further by treating *p*-quinophenol with methyl iodide and potassium hydroxide, or directly by the method of Skraup fro ı *p*-amidoanisol (*p*-anisidine).

Of the monoxyquinolines which have the hydroxyl group in the pyridine ring, two are known, *carbostyril* (α-oxyquinoline) and *kynurine* (γ-oxyquinoline). These, like the corresponding oxypyridines (p. 18), occur in two tautomeric forms, the hydroxyl- and the ketone-form.



α-Oxyquinoline α-Quinolone
Carbostyril

γ-Oxyquinoline γ-Quinolone
Kynurine

[21] Skraup, M. 4, 695.
[22] Butlerow and Wischnegradsky, B. 12, 2094.
[23] Skraup, M. 3, 557; 6, 760.

Carbostyril was first obtained in 1852 by Chiozza[24] from the reduction of *o*-nitrocinnamic acid and it is consequently the inner anhydride of *o*-amidocinnamic acid:

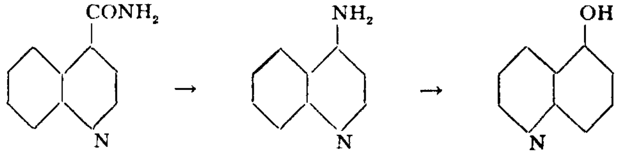
$$C_6H_4\left\langle\begin{matrix}CH{=}CH\\ \quad\ \ |\\ NH_2\ COOH\end{matrix}\right. \rightarrow C_6H_4\left\langle\begin{matrix}CH{=}CH\\ \quad\ \ |\\ N{=\!=}COH\end{matrix}\right. \text{ or } C_6H_4\left\langle\begin{matrix}CH{=}CH\\ \quad\ \ |\\ NH{-}CO\end{matrix}\right. + H_2O$$

It is also easily formed by the direct oxidation of quinoline with hypochlorous acid, or "chloride of lime";[25] it is further produced by heating α-chlorquinoline and α-bromquinoline with water to 120°.[26] The base crystallizes in prisms with one molecule of water; in the anhydrous condition it melts at 199–200°.

Kynurine was prepared in 1872 by Schmiedeberg and Schultzen[27] by distilling kynurenic acid—an acid discovered by Liebig in 1853 in the urine of the dog.

It is also formed by the oxidation of cinchonine, of cinchonidine, and of cinchoninic acid with chromic acid.[28]

It has been synthesized further by Claus and Howitz[29] from the amide of cinchoninic acid. On treatment with sodium hypobromite (Hofmann's reaction) this is converted into γ-amidoquinoline, which when diazotized yields kynurine:



Amide of cinchoninic acid — γ-Amidoquinoline — Kynurine

Kynurine crystallizes with three molecules of water in prisms which melt at 201°.

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[24] Chiozza, A. **83**, 118.

[25] Einhorn and Lauch, B. **19**, 53; A. **243**, 342. Erlenmeyer and Rosenhek, B. **18**, 3295; **19**, 489.

[26] Friedländer and Ostermaier, B. **15**, 335. Claus and Pollitz, J. pr. **41**, 41.

[27] Schmiedeberg and Schultzen, A. **164**, 158.

[28] Skraup, M. **7**, 517; **9**, 783; **10**, 726.

[29] Claus and Howitz, J. pr. **50**, 232.

CHAPTER VI.

METHYLQUINOLINES, $C_{10}H_9N$—$C_9H_6N(CH_3)$.

THE seven methylquinolines theoretically possible are all known. Four of these isomeric bases which have the methyl group in the benzol ring of the quinoline are commonly known as *toluquinolines*.

The toluquinolines were prepared by Skraup[1] by replacing, in his well-known synthesis, the aniline with the three toluidines. The methylquinolines resulting are liquids which in odor and in other properties in general resemble quinoline itself. On oxidation there are formed first the quinoline monocarboxylic acids and then quinolinic acid.

1. *o-Toluquinoline* boils at 248°.
2. *p-Toluquinoline* boils at 257–258°.
3. *m-Toluquinoline* boils at 250°.

The last base forms the chief product of the reaction between glycerine and *m*-toluidine. Skraup established the *m*-position of the methyl group in this derivative by oxidizing it to *m*-quinoline carboxylic acid (page 102).

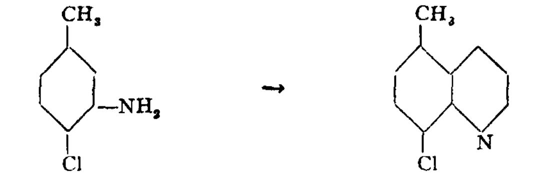
4. The fourth *toluquinoline*, boiling at 250°, is formed as a side-product in the synthesis of *m*-toluquinoline. Since this base is not identical with any of the other toluquinolines, it must be the *ana*-derivative.

To this indirect proof Gattermann and Kaiser[2] have added a direct one. They subjected *p*-chlor-*m*-toluidine to the reaction

[1] Skraup, M. 2, 153; 3, 381; 7, 139.

[2] Gattermann and Kaiser, B. 18, 2602, 3245. Lellmann and Alt, A. 237, 307.

of Skraup. The quinoline base thus obtained must be *o*-chlor-*a*-toluquinoline:

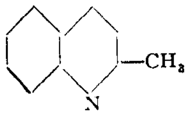


p-Chlor-*m*-toluidine   *o*-Chlor-*a*-toluquinoline

On reduction of this latter substance with hydriodic acid, the chlorine atom is replaced by hydrogen and a base is obtained which is identical with the *a*-toluquinoline obtained above by Skraup.

The following methylquinolines have the alkyl group in the pyridine ring:

5. *Quinaldine* (α-methylquinoline):



Quinaldine is found with quinoline in coal-tar.[3] It is a liquid which boils at 247°.

Doebner and von Miller[4] synthesized it in 1881 by employing a modification of Skraup's synthesis, in which they replaced the glycerine with glycol. They soon found, however, that the glycol could be advantageously exchanged for acetaldehyde, that further the addition of nitrobenzol was superfluous, since the oxygen necessary for the reaction was afforded by a third molecule of the acetaldehyde. In fact, the most effective method for the synthesis of quinaldine appeared to be the warming on the water-bath of a mixture of aniline, paraldehyde, and concentrated hydrochloric acid.

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[3] Jacobsen and Reimer, B. **16**, 1082.

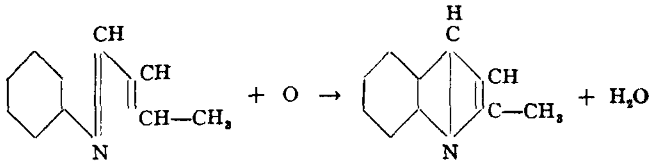
[4] Doebner and von Miller, B. **14**, 2812; **15**, 3075; **16**, 2464; **17**, 1698; **18**, 1646; **24**, 1720; **25**, 2072.

The mechanism of this reaction has not, as yet, been made entirely clear; it is probably analogous to that in the synthesis of Skraup. Under the dehydrating influence of the concentrated hydrochloric acid two molecules of aldehyde condense to crotonaldehyde. The latter then unites with the aniline to form crotonylene-aniline, which by loss of two hydrogen atoms gives rise to quinaldine:

$$\text{I.}\quad \underset{\text{Acetaldehyde}}{2CH_3{-}CHO} \rightarrow \underset{\text{Crotonaldehyde}}{CH_3CH{=}CHCHO} + H_2O.$$

$$\text{II.}\quad \underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Crotonaldehyde}}{CHO{-}CH{=}CH{-}CH_3} \rightarrow$$

$$\underset{\text{Crotonylene-aniline.}}{C_6H_5N{=}CH{-}CH{=}CH{-}CH_3} + H_2O.$$

III. 

Crotonylene-aniline Quinaldine

Skraup,[5] indeed, succeeded in synthesizing quinaldine by heating together aniline, crotonaldehyde, nitrobenzol, and sulphuric acid.

The synthesis of Doebner and von Miller like that of Skraup is of general application. If the aniline is replaced by other aromatic amines, or the aldehyde by other aldehydes or ketones, a large number of quinoline derivatives may be obtained.

Quinaldine may be prepared by a number of other synthetic processes, of which we may mention the following as among the most important:

a. By heating lactic acid with aniline and zinc chloride, or with a mixture of aniline, nitrobenzol, and sulphuric acid.[6] This reaction is a modification of the synthesis of Doebner and Miller,

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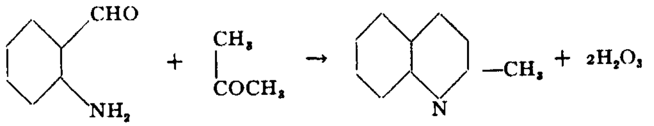
[5] Skraup, B. 15, 897.
[6] Wallach and Wüsten, B. 16, 2007. Pictet and Duparc, B. 20, 3415.

since the lactic acid here decomposes into aldehyde and formic acid.

b. By the condensation of *o*-amidobenzaldehyde with acetone:[7]

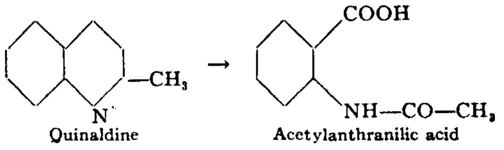


c. By reducing *o*-nitrobenzylidene-acetone, $(NO_2)C_6H_4—CH=CH—CO—CH_3$, a condensation-product of *o*-nitrobenzaldehyde and acetone.[8]

d. By heating ethylacetanilide with zinc chloride to 250°.[9]

e. By heating α-methylindol with bromoform and sodium alcoholate and treating the β-bromquinaldine thus obtained with hydriodic acid and phosphorus.[10]

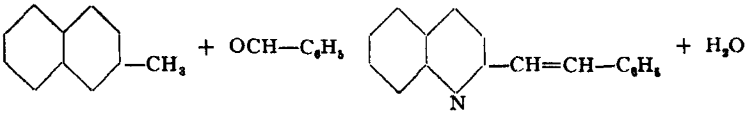
The constitution of quinaldine is established by its conversion to acetylanthranilic acid on oxidation with potassium permanganate:



Chromic acid acts on the base somewhat differently; there is formed *quinaldic acid* (α-quinoline carboxylic acid).[11]

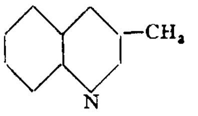
Like all pyridine derivatives having a methyl group in the α-position, quinaldine reacts easily with aldehydes and ketones to form unsaturated derivatives:[12]

[7] Friedländer and Gohring, B. 16, 1833.
[8] Drewsen, B. 16, 1953.
[9] Pictet and Bunzl, B. 22, 1847.
[10] Magnanini, B. 20, 2608; 21, 1940.
[11] Doebner and von Miller, B. 15, 3075; 16, 2472.
[12] Jacobsen and Reimer, B. 16, 513, 1082, 1892, 2602, 2942. Wallach and Wüsten, B. 16, 2007.

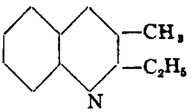


Quinaldine Benzaldehyde Benzylidene-quinaldine

6. *β-Methylquinoline:*



β-Methylquinoline was synthesized by Doebner and von Miller[13] in 1884. If, in their general synthetic process for quinaldine, the acetaldehyde is exchanged for propionaldehyde, there is formed *β-methyl-α-ethylquinoline:*

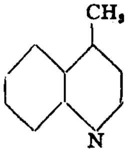


On oxidation of this compound, the ethyl group which is first attacked is changed to the carboxyl group. When the calcium salt of the acid thus obtained is subjected to dry distillation it yields a new base. This is undoubtedly β-methylquinoline, since on oxidation it is converted into β-quinoline carboxylic acid (page 104).

von Miller and Kinkelin[14] later prepared the same base directly by heating a mixture of aniline, propionaldehyde, and formaldehyde with hydrochloric acid.

β-Methylquinoline crystallizes in prisms which melt at 10–14°; its boiling-point is 250°.

7. *Lepidine* (γ-Methylquinoline):



This base was isolated by Williams in 1855 from the product resulting from the distillation of cinchonine with potassium hy-

[13] Doebner and von Miller, B. 17, 1712; 18, 1640.

[14] von Miller and Kinkelin, B. 20, 1916.

droxide. The year following, the same investigator [15] found in coal-tar a base of the same composition, which he regarded as an isomer of lepidine and which he named ***iridoline.*** Later it was shown that the two bodies were identical.

Lepidine has further been obtained:

a. By distilling cinchonine with lead oxide.[16]

b. By heating cinchene and dihydrocinchene, decomposition-products of cinchonine, with acetic acid to 200°, or with a solution of phosphoric acid to 180°.[17]

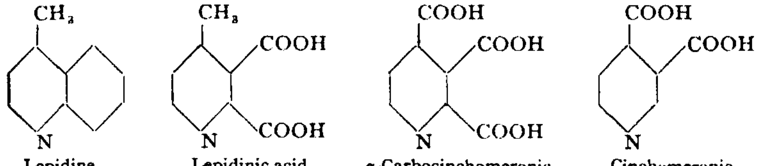
c. By distilling over zinc-dust tetrahydrocinchoninic acid, a reduction-product of cinchoninic acid.[18]

d. By the distillation over zinc-dust of α-oxylepidine, a body obtained by the condensation of aniline with aceto-acetic ester.[19]

e. By the condensation of *o*-amido-acetophenone and paraldehyde in the presence of caustic soda.[20]

f. By the condensation of aniline, acetone, and formaldehyde by means of hydrochloric acid.[21]

The constitution of lepidine follows from its oxidation by chromic acid to cinchoninic acid (γ-quinoline carboxylic acid, p. 104). When, however, the base is oxidized with potassium permanganate it is not the methyl group which is first attacked, but the benzol ring, and there are formed successively lepidinic acid (γ-methylquinolinic acid), α-carbocinchomeronic acid, and cinchomeronic acid:



Lepidine — Lepidinic acid — α-Carbocinchomeronic acid — Cinchomeronic acid

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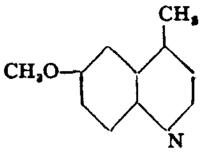
[15] Williams, J. 1855, 550; 1856, 536; 1863, 431.
[16] Hoogewerff and van Dorp, R. 2, 1; B. 13, 1639; 16, 1381.
[17] Königs, B. 23, 2669; 27, 900, 1501, 2290.
[18] Weidel, M. 3, 75.
[19] Knorr, B. 16, 2593; A. 236, 69.
[20] O. Fischer, J 1885, 1013.
[21] Beyer, J. pr. 32, 125; 33, 393.

Lepidine is a liquid which boils at 255°.

A *tribromoxylepidine* of unknown constitution has been obtained by Comstock and Königs [22] from the action of bromine on the sirupy oxidation-products of cinchonine and cinchene.

p-Methoxylepidine,



forms one of the decomposition-products of quinine. It was obtained by Königs [23] by treating quinine with potassium hydroxide and by heating quinene to 180° with phosphoric acid. It crystallizes with one molecule of water in needles which melt at 50–52°.

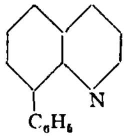
[22] Comstock and Königs, B. 17, 1984.
[23] Königs, B. 23, 2669; 27, 900.

CHAPTER VII.

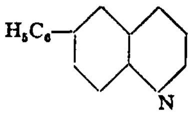
PHENYLQUINOLINES, $C_{15}H_{11}N—C_9H_6N(C_6H_5)$.

Of the seven monophenylquinolines theoretically possible five are now known. Two of these have the phenyl group in the benzol ring and three have this group in the pyridine ring.

1, 2. *o-Phenylquinoline* and *p-phenylquinoline*,



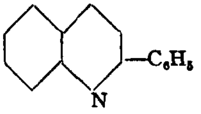
o-Phenylquinoline



p-Phenylquinoline

have been prepared by the method of Skraup from *o*- and *p*-amidodiphenyl respectively.[1] The *o*-derivative is a liquid which boils at 270–276° under 80 mm. pressure; the *p*-derivative crystallizes in leaflets which melt at 110–111°; it boils under ordinary pressure at 360°.

3. *α-Phenylquinoline*,



[1] La Coste and Sorger, B. **15**, 562; A. **230**, 1.

may be synthesized by several methods analogous to those which are employed in the preparation of quinoline and quinaldine:

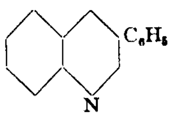
a. The condensation of aniline with cinnamic aldehyde and nitrobenzol by means of sulphuric acid[2] or of hydrochloric acid.[3]

b. The condensation of acetophenone with *o*-amidobenzaldehyde[4] or with formanilide.[5]

c. The reduction of *o*-nitrobenzylidene-acetophenone.[6]

α-Phenylquinoline crystallizes from alcohol in needles which melt at 84°. By oxidation it is converted into benzoylanthranilic acid.

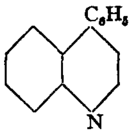
4. *β-Phenylquinoline,*



is formed by the condensation of *o*-amidobenzaldehyde with phenylacetaldehyde by means of caustic soda.

It is an oil which has as yet been little studied.[4]

5. *γ-Phenylquinoline,*



presents greater interest for us than its isomers, since, according to Königs, it forms the mother-substance of the cinchona-alkaloids. Its physiological action, in fact, somewhat resembles that of quinine.[7] It forms needles of melting-point 61–62°.

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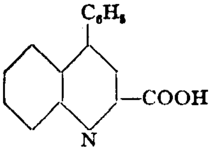
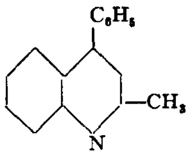
[2] Grimaux, C. r. 96, 584.
[3] Doebner and von Miller, B. 16, 1664; 19, 1194.
[4] Friedländer and Gohring, B. 16, 1833.
[5] Pictet and Barbier, Bl. [3] 13, 26.
[6] Goldschmidt, B. 28, 986.
[7] Tappeiner, *Münchener med. Wochenschrift*, 43, 1.

γ-Phenylquinoline is prepared by heating *γ-phenylquinaldic acid,*



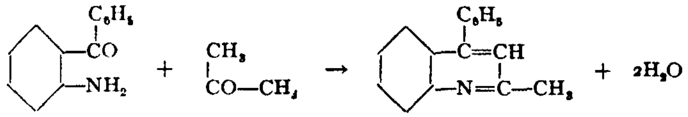
above its melting-point (171°). By this treatment the carboxyl group is eliminated.

γ-Phenylquinaldic acid is in turn obtained by the oxidation of *γ-phenylquinaldine:*

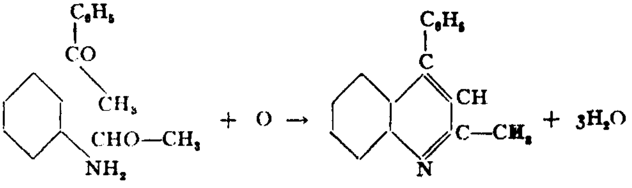


The synthesis of the last derivative is easily effected by a number of methods analogous to those employed in the preparation of quinaldine:

a. The action of alcoholic potash on a mixture of *o*-amidobenzophenone and acetone:[8]



b. The condensation of aniline with acetophenone and paraldehyde by means of hydrochloric acid:[9]



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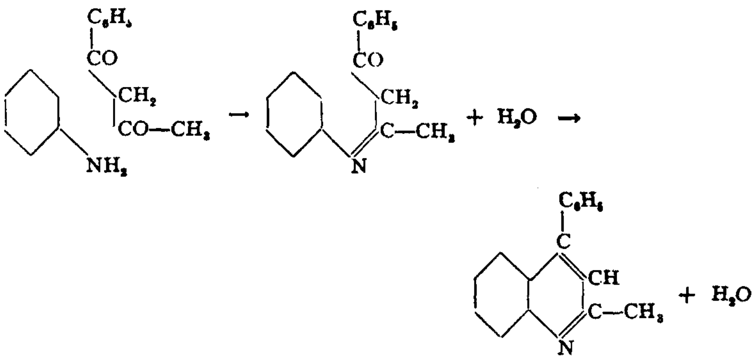
[8] Königs and Geigy, B. 18, 2400.
[9] Beyer, J. pr. 33, 393.

c. The action of sulphuric acid on the anilide of benzoylacetone:[10]



Phenylquinaldine crystallizes in tablets melting at 100°. By the action of chromic acid it is, as indicated above, oxidized to γ-phenylquinaldic acid (γ-phenylquinoline-α-carboxylic acid).

Oxyphenylquinolines, or Quinoline Phenols—By the dry distillation of the silver salt of ethylhomoapocinchenic acid (a decomposition-product of cinchonine) Königs[11] in 1893 obtained a derivative of the formula $C_{17}H_{15}NO$ (melting-point 80–81°). The behavior of this substance indicated that it was the ethyl ether of a phenol. Heated with hydrobromic acid, it was decomposed into ethyl bromide and a substance, $C_{15}H_{11}NO$ (melting-point 208°), which possessed all the properties of a phenol.

Oxidation of this last body gave rise to cinchoninic acid (γ-quinoline carboxylic acid).

From these observations it follows that the two substances in question are respectively the ethoxyl and hydroxyl derivatives of γ-phenylquinoline, and further that both the substituting groups are in the phenyl radical and not in the quinoline nucleus. Königs accordingly assigned them the following formulæ and

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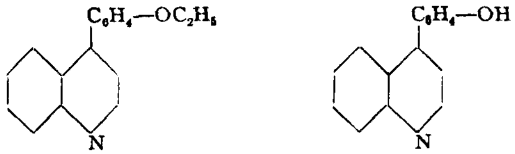
[10] Beyer, B. 20, 1767.
[11] Königs, B. 26, 713.

gave them the names *γ-quinoline phenetol* and *γ-quinoline phenol* (γ-phenol quinoline):



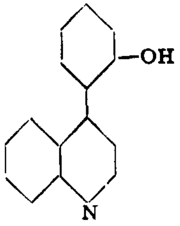
The constitution of both these derivatives remained for a long time incompletely determined, for corresponding to each of the above formulæ three isomers are possible according to the position of the $—OC_2H_5$, or —OH group, with reference to the γ-carbon atom of the quinoline.

A mixture of these three isomers was, indeed, obtained by Königs and Nef,[12] when they attempted to synthesize phenol quinoline from phenylquinoline by introducing in the latter the nitro group and subsequently replacing this with hydroxyl. One of these isomers proved identical with the phenol quinoline derived from cinchonine. But this synthesis, while it confirmed the accuracy of the results previously obtained, threw no light upon the position of the hydroxyl group.

The question, however, was solved shortly afterwards by a synthesis of phenol quinoline which was effected by Besthorn and Jaeglé.[13] These investigators employed the process of Beyer (*c*, page 99) and replaced the benzoylacetone with ortho-, meta-, and para-oxybenzoylacetone. The phenol quinoline thus prepared from *o*-oxybenzoylacetone proved to be identical with the decomposition-product of cinchonine; the other two isomers from *m*- and *p*-oxybenzoylacetone were identical with the two remaining phenol quinolines which had been obtained by Königs and Nef.

[12] Königs and Nef, B. 19, 2427; 20, 622.
[13] Besthorn and Jaeglé, B. 27, 907, 3035; 28, Ref. 400.

The phenol quinoline from cinchonine has, accordingly, the following constitution:



CHAPTER VIII.

MONOCARBOXYLIC ACIDS OF QUINOLINE, $C_{10}H_7NO_2—C_9H_6N(COOH)$.

THE seven quinoline monocarboxylic acids theoretically possible are all known.

Those acids which have the carboxyl group in the benzol ring are known as the *quinoline benzocarboxylic acids.* Three of these latter are prepared by treating the three amidobenzoic acids with glycerine and sulphuric acid.[1] They are further obtained by converting the three amidobenzol sulphonic acids into the quinoline sulphonic acids, then distilling these with potassium cyanide, and finally saponifying the cyanquinolines thus formed.[2]

1. *o-Quinoline carboxylic acid* forms needles which melt at 187°.

2. *m-Quinoline carboxylic acid* also occurs in needles which melt at 248–249°. It was prepared by Skraup and Brunner[3] by oxidizing *m*-toluquinoline with chromic acid. It is also formed by oxidizing *β*-diquinolyl $(C_9H_6N)_2$.[4]

3. *p-Quinoline carboxylic acid* crystallizes in leaflets and melts at 291–292°.

4. *a-Quinoline carboxylic acid* occurs as a powder which melts at 357°. It is prepared from *m*-amidobenzoic acid and from *m*-aniline sulphonic acid. According to its mode of forma-

[1] Schlosser and Skraup, M. 2, 519.

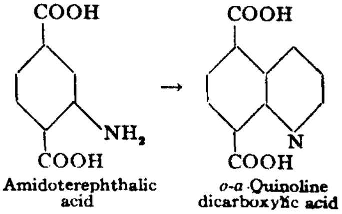
[2] Bedall and O. Fischer, B. 14, 2574; 15, 683. O. Fischer and Willmack, B. 17, 440. O. Fischer and Körner, B. 17, 765. La Coste, B. 15, 196.

[3] Skraup and Brunner, M. 7, 139.

[4] Fischer and van Loo, B. 17, 1899; 19, 2471.

tion, the carboxyl group may stand either in the meta- or the ana- position. This position has been very ingeniously determined in the following manner by Skraup and Brunner:[4]

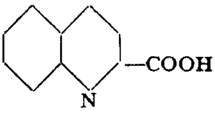
When amidoterephthalic acid is treated with glycerine and sulphuric acid it forms a quinoline dicarboxylic acid which must be an ortho-ana-derivative:



Now this acid, on being heated to 270°, loses carbon dioxide and gives rise to two quinoline monocarboxylic acids. One of these is the ortho-acid; the other is identical with that acid which is obtained from meta-amidobenzoic acid. This latter must consequently be ana-quinoline carboxylic acid.

The three remaining quinoline monocarboxylic acids have the carboxyl group attached to the pyridine nucleus.

5. *Quinaldic acid* (α-quinoline carboxylic acid):

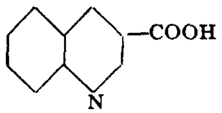


Doebner and von Miller[5] prepared quinaldic acid by oxidizing quinaldine with chromic acid. This mode of formation establishes the position of the carboxyl group. The acid is further formed by the oxidation of α-ethylquinoline.[6]

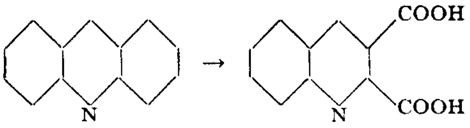
It crystallizes with two molecules of water in needles which melt at 156° and at a higher temperature decompose into quinoline and carbon dioxide. On oxidation with potassium permanganate, quinaldic acid yields carboisocinchomeronic acid (page 68).

[5] Doebner and von Miller, B. 16, 2472; 24, 1900.
[6] Reher, B. 19, 2995.

6. *β-Quinoline carboxylic acid:*



In 1880 Graebe and Caro[7] by the oxidation of acridine with potassium permanganate obtained a dicarboxylic acid of quinoline which they called *acridic acid:*



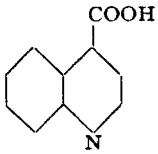
Acridine Acridic acid

If now this is heated to 120–130°, it loses a molecule of carbon dioxide and forms a monobasic acid which melts at 273° and which must be either α- or β-quinoline monocarboxylic acid. Since we have already identified quinaldic acid as the α-derivative, the acid of Graebe and Caro is consequently β-quinoline carboxylic acid.

This acid is further formed by oxidizing with chromic acid β-methylquinoline[8] and β-ethylquinoline.[9]

Treated with potassium permanganate, β-quinoline carboxylic acid yields carbodinicotinic acid (page 70).

7. *Cinchoninic acid* (γ-quinoline carboxylic acid):



Cinchoninic acid was found in 1870 by Caventou and Willm[10] in the products resulting from the oxidation of cinchonine with

[7] Graebe and Caro, B. 13, 100.
[8] Doebner and von Miller, B. 18, 1640.
[9] Riedel, B. 16, 1609.
[10] Caventou and Willm, A. Supl. 7, 247.

potassium permanganate. Weidel[11] and Königs[12] obtained it also by treating the same alkaloid with nitric or chromic acid.

It is formed further by the oxidation of several other cinchona-alkaloids,[13] by the oxidation of lepidine,[14] and of γ-ethylquinoline.[15]

Cinchoninic acid crystallizes with one molecule of water in needles, or with two in prisms; its melting-point is 253–254°. Heated with lime it is converted into quinoline. Potassium permanganate oxidizes it to α-carbocinchomeronic acid (page 67), nitric acid to cinchomeronic acid (page 62), and chromic acid to kynurine (page 87).

The carboxyl group in cinchoninic acid must occupy the γ-position, since the other positions possible are taken by the six isomeric acids already discussed.

In 1879 Skraup[16] obtained a derivative of γ-quinoline carboxylic acid by oxidizing quinine with chromic acid. There is thus formed a monobasic acid of the formula $C_{11}H_9NO_3$ which he named *quininic acid.* This acid crystallizes in prisms which melt with decomposition at 280°. Heated with hydrochloric acid to 220–230°, quininic acid loses a methyl group and is converted into *xanthoquininic acid:*

$$\underset{\text{Quininic acid}}{C_{11}H_9NO_3} + HCl \rightarrow \underset{\text{Xanthoquininic acid}}{C_{10}H_7NO_3} + CH_3Cl$$

The latter acid melts with decomposition at 310°. At this temperature the carboxyl group is lost and there is formed a derivative, C_9H_7NO, which is identical with *p*-oxyquinoline (page 87).

Xanthoquininic acid is accordingly the carboxyl derivative of *p*-oxyquinoline, and quininic acid that of *p*-methoxyquinoline. The position of the carboxyl group in both these acids is shown

[11] Weidel, A. **173**, 76.

[12] Königs, B. **12**, 97.

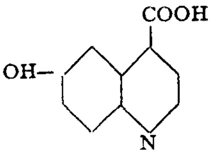
[13] Skraup, B. **12**, 230; M. **10**, 220. Forst and Böhringer, B. **14**, 436; **15**, 519. Königs, B. **17**, 1984; **26**, 713; **27**, 900. Claus and Weller, B. **14**, 1921. Freund and Rosenstein, A. **277**, 277. Schniderschitsch, M. **10**, 51. Strache, M. **10**, 642.

[14] Weidel, M. **3**, 79. Hoogewerff and van Dorp, R. **2**, 1.

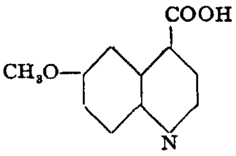
[15] Reher, B. **19**, 2995.

[16] Skraup, M. **2**, 589; **4**, 695; B. **12**, 1106; **16**, 2684.

by the fact that quininic acid is oxidized by potassium permanganate to α-carbocinchomeronic acid (page 67).



Xanthoquininic acid



Quininic acid

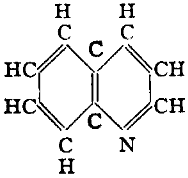
CHAPTER IX.

ISOQUINOLINE.

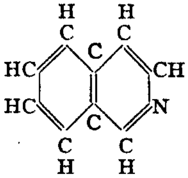
Isoquinoline was discovered in 1885 by Hoogewerff and van Dorp [1] in coal-tar, where it is found in small quantities with its isomer, quinoline. The separation of the two bases is effected through their sulphates, that of isoquinoline being much less soluble than that of quinoline.

Isoquinoline is a colorless liquid (boiling-point 240°) of quinoline-like odor; indeed, in almost all its properties it closely resembles its isomer. It differs from quinoline most markedly in its high melting-point, which lies at +22°; in the solid condition it forms well-defined, white, tabular crystals.

Isoquinoline, like quinoline, results from the union of a pyridine ring with a benzol ring. While in the case of quinoline the benzol nucleus is attached to the $\alpha\beta$-carbon atoms of pyridine, in the case of isoquinoline the points of attachment are the $\beta\gamma$-carbon atoms.



Quinoline



Isoquinoline

We may then regard isoquinoline as a naphthalene in which one of the CH-groups in the β-position has been replaced by a

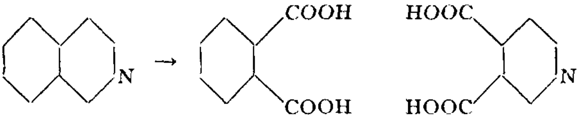
[1] Hoogewerff and van Dorp, R. 4, 125; 5, 305.

nitrogen atom. A synthesis of isoquinoline from naphthalene has, indeed, been effected.[2]

Isoquinoline is of particular interest, since it has been shown that from it are derived several of the important alkaloids, as papaverine, narcotine, and hydrastine.

The constitution of isoquinoline follows from its characteristic behavior on oxidation.

Treated with an alkaline solution of potassium permanganate, there is obtained a mixture of phthalic and cinchomeronic acids:[3]

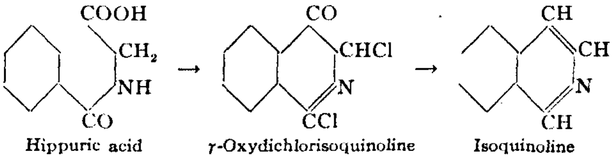


Isoquinoline Phthalic acid Cinchomeronic acid

Here, unlike the action in the case of quinoline, the benzol and pyridine nuclei are attacked at the same time by the oxidizing agent. If, however, a neutral solution of potassium permanganate is employed, the benzol nucleus remains intact and there is formed phthalimide.[4]

The constitutional formula assigned to isoquinoline is further supported by the various syntheses of the base. The following are the most important of these given in their chronological order:

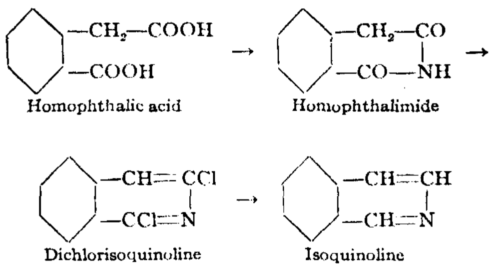
1. Schwanert[5] observed in 1859 that hippuric acid is converted by the action of phosphorus pentachloride into a body of the formula $C_9H_5Cl_2NO$. In 1886 Rügheimer[6] showed that this was an oxydichlorisoquinoline; on reducing this derivative with hydriodic acid, he obtained isoquinoline:



Hippuric acid γ-Oxydichlorisoquinoline Isoquinoline

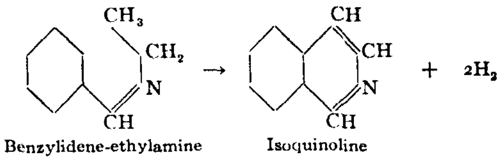
[2] Bamberger and Lodter, B. 26, 1833.
[3] Hoogewerff and van Dorp, R. 4, 285.
[4] Goldschmiedt, M. 9, 675.
[5] Schwanert, A. 112, 59.
[6] Rügheimer, B. 19, 1169; 21, 3321.

2. The same year Gabriel[7] discovered a much better method for the synthesis of isoquinoline. The ammonium salt of homophthalic acid on distillation yields homophthalimide. Phosphorus oxychloride converts this into dichlorisoquinoline, which is reduced by hydriodic acid to isoquinoline:



Homophthalimide is also converted into isoquinoline by distillation over zinc-dust.[8]

3. In 1892 Pictet and Popovici[9] succeeded in synthesizing isoquinoline directly by passing the vapor of benzylidene-ethylamine through a tube heated to redness:



4. An interesting method of preparing isoquinoline from naphthalene was discovered in the same year by Bamberger and Kitschelt,[10] and almost at the same time by Zincke.[11]

On treatment with hypochlorous acid, β-naphthoquinone

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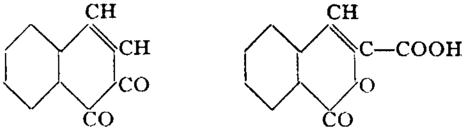
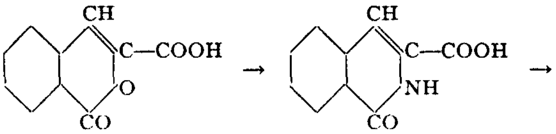
[7] Gabriel, B. **19**, 1655, 2355.
[8] Le Blanc, B. **21**, 2299.
[9] Pictet and Popovici, B. **25**, 733.
[10] Bamberger and Kitschelt, B. **25**, 1138.
[11] Zincke, B. **25**, 1493.

undergoes oxidation and molecular rearrangement to isocoumarin carboxylic acid:

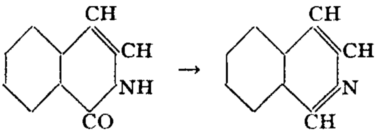


β-Naphthoquinone Isocoumarin carboxylic acid

This acid contains a pyrone ring (page 20) and consequently easily exchanges its oxygen for the NH-group, thus forming isocarbostyril carboxylic acid. On being heated this latter acid loses its carboxyl group and is converted into isocarbostyril, which can be reduced to isoquinoline by distillation with zinc-dust:

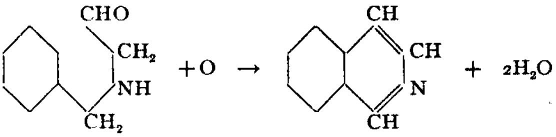


Isocoumarin carboxylic acid Isocarbostyril carboxylic acid



Isocarbostyril Isoquinoline

5. Isoquinoline is further formed by the action of concentrated sulphuric acid on benzylamidoacetaldehyde,[12] or on benzylidene-amidoacetal, $C_6H_5—CH{=}N—CH_2—CH(OC_2H_5)_2$:[13]



Benzylamidoacetaldehyde Isoquinoline

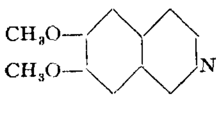
[12] E. Fischer, B. **26**, 764.
[13] Pomeranz, M. **14**, 116; **15**, 299.

6. Bamberger and Goldschmidt[14] obtained isoquinoline by heating with phosphoric anhydride both the isomeric oximes of cinnamic aldehyde, $C_6H_5CH{=}CH{-}CH{=}NOH$. In this case a molecular rearrangement must occur similar to that of Beckmann.

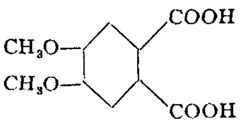
Substitution-products of Isoquinoline.

Of the numerous substitution-products of isoquinoline we shall mention here only those which are obtained as products of decomposition of the natural alkaloids.

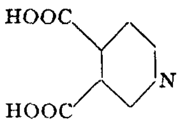
1. *m-p-Dimethoxylisoquinoline* is formed by fusing papaverine with caustic potash.[15] Its constitution is shown by the products of its oxidation with potassium permanganate. There is thus obtained a mixture of metahemipinic (page 288) and cinchomeronic acids (page 62):



m-p-Dimethoxylisoquinoline

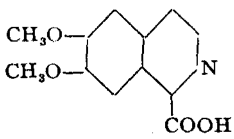


Metahemipinic acid



Cinchomeronic acid

2. A carboxyl derivative of the above base is formed by the oxidation of papaverine with potassium permanganate; this is *m-p-dimethoxylisoquinoline-α-carboxylic acid:*[16]

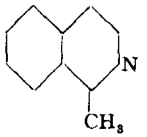


Its constitution is shown by its yielding, on more energetic oxidation, metahemipinic and α-carbocinchomeronic acids.

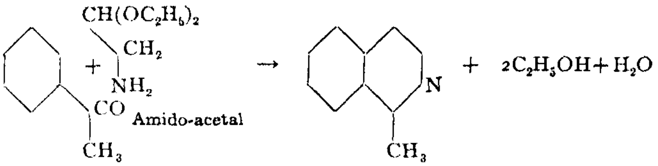
3. A methylisoquinoline has been prepared by Krauss[17] by

[14] Bamberger and Goldschmidt, B. 27, 1954, 2795.
[15] Goldschmiedt, M. 7, 485; 9, 327.
[16] Goldschmiedt, M. 6, 954; 8, 510.
[17] Krauss, M. 11, 350.

distilling over zinc-dust papaveroline, a product of the decomposition of papaverine (page 286). It probably possesses the formula,

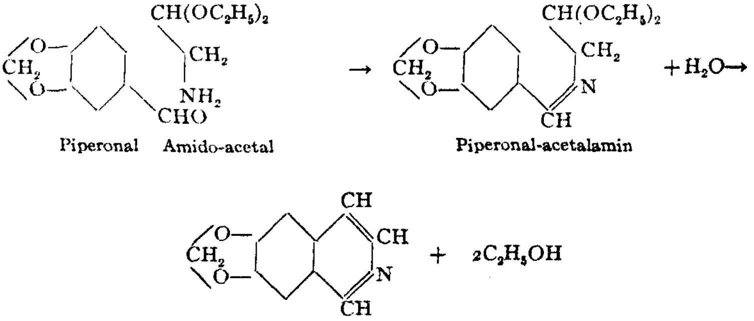


although in the properties of its salts it differs somewhat from the base of the same constitution, which was synthesized by Pomeranz[18] by the action of concentrated sulphuric acid on a mixture of amido-acetal and acetophenone:



Acetophenone α-Methylisoquinoline

4. Fritsch[19] has synthesized a *methylene-dioxyisoquinoline* by condensation of piperonal (page 145) with amido-acetal and treatment of the resulting product with sulphuric acid:



Methylene-dioxyisoquinoline

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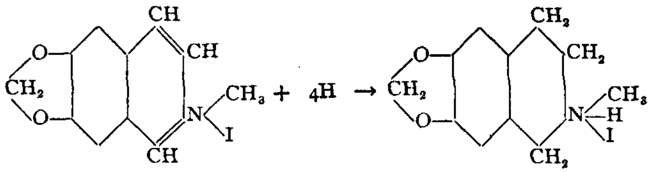
[18] Pomeranz, M. 15, 299.
[19] Fritsch, A. 286, 1

When the methyl iodide of this last base is reduced with tin and hydrochloric acid, there is obtained a *methylene-dioxy-methyltetrahydroisoquinoline*, which is identical with hydrohydrastinine (page 317):



Methylene-dioxyisoquinoline methiodide — Hydrohydrastinine hydriodide

SECOND PART.

THE NATURAL ALKALOIDS.

CHAPTER X.

DISTRIBUTION AND GENERAL PROPERTIES OF THE NATURAL ALKALOIDS.

Occurrence.—The alkaloids are found distributed throughout the vegetable kingdom in almost all the different plant families. Some families, indeed, are marked by the large number of alkaloids which they produce; such, for example, are the Rubiaceæ, Apocynaceæ, Solanaceæ, Papaveraceæ, and Leguminosæ. In others equally important, however, as the Labiatæ, Rosaceæ, and Orchidaceæ, no alkaloids have as yet been found.

The alkaloids occurring in any case in the same plant generally bear the closest chemical relation to one another. Often they form a homologous series, frequently they are isomers, or even stereoisomers. In other cases the only difference between these bodies is the amount of hydrogen or oxygen which they contain, so that by reduction or oxidation they can be converted into one another. There seems to be thus an intimate connection between the properties on which the classification of plants is based and those which should naturally determine the classification of the alkaloids. The interpretation of such relations will be much simpler, however, when the molecular structures of a much larger number of the plant bases are definitely known. The same alkaloid is rarely met in different

families, but not infrequently an alkaloid is characteristic of a family, or even of a species.

There is, however, a small number of weak bases of no particular physiological activity which are found in various plants bearing no botanical relation to one another. These bases may be divided according to their chemical constitution into three different groups, of which the representative members are xanthine, choline, and asparagine. They differ from the remaining alkaloids, however, in that they appear to be not *assimilation-products* of the plant organism, but *decomposition-products* of more complicated derivatives.

The alkaloids are rarely found in the free condition in nature, but usually in combination with such acids as commonly occur in plants, as, for example, malic, citric, oxalic, succinic, or tannic acid. In some cases certain alkaloids are associated with characteristic acids. Thus with the cinchona alkaloids is found quinic acid; with opium, meconic acid; with aconitine, aconitic acid.

Physical Properties.

By far the greater number of the plant bases are solids, chiefly crystalline in character, though some are amorphous; a few are liquids at the ordinary temperature.

The solubility of the alkaloids in the ordinary solvents is quite variable. The most are insoluble or little soluble in cold water; some others, on the other hand, are easily soluble in this liquid. In general they dissolve readily in alcohol, somewhat less readily in ether, chloroform, and benzol, and still less readily in ligroin.

The free alkaloids as well as their simple salts are in the pure condition almost all colorless. Among the few which are distinctly colored are berberine, sinapine, harmaline (yellow), and sanguinarine (red). The phenomenon of fluorescence is shown by some, particularly by quinine.

The solutions of the free alkaloids or their salts are in general bitter to the taste, or sharp and burning. The most of the alka-

loids show an alkaline reaction toward litmus. In some cases the presence of acid groups, such as carboxyl or hydroxyl, produces a neutral or even a slightly acid reaction.

Almost all the plant bases are optically active, although a few are indifferent in their behavior toward polarized light. Of these latter, some owe their optical inactivity to the absence of an asymmetric carbon atom in the molecule (compare piperine, papaverine, narceïne, etc.); others, as atropine and lupinine, are racemic mixtures and can be separated into their optically active constituents.

General Chemical Reactions.

The investigations which aim to determine the constitution of any organic compound take two distinct directions. They must in the first place establish the chemical nature of the compound in question by ascertaining the function of every atom in the molecule. In the second place they must transform the compound into simpler derivatives of known constitution. This double aim can be attained in the case of the natural alkaloids in various ways. There are, however, certain general methods of investigation which have been successfully employed in studying these bases and certain characteristic reactions which are common to the different representatives of this class of bodies. We will first briefly consider these before discussing in detail the results which have been obtained for the individual alkaloids.

Oxygen.—Of the alkaloids known, fourteen only do not contain oxygen. These are: conine, methylconine, γ-coniceïne, nicotine, nicotimine, nicoteïne, nicotelline, sparteïne, lupinidine, curarine, conessine, aribine, adenine, and hymenodictine.

All the others contain this element. Consequently it is of the utmost importance to determine the function of the oxygen in the various alkaloids.

1. The oxygen is often present in a hydroxyl group. In this case by the action of acetic anhydride, acetyl or benzoyl chloride, there are prepared acetyl or benzoyl derivatives, whose analysis enables us to determine the number of hydroxyl groups in the

original substance. It has thus been shown, for example, that cinchonine contains one, morphine two, aconitine three, and solanine six hydroxyl groups.

These hydroxyl groups are generally alcoholic in character, although not infrequently they are of the phenol type. Thus morphine and cupreine are true phenols; they dissolve in alkalies and are reprecipitated by carbonic acid; in alkaline solution they are converted by the alkyl iodides into esters, etc.

The most of the alkaloids containing hydroxyl readily lose the elements of water and pass into unsaturated derivatives, when they are acted upon by dehydrating agents (concentrated hydrochloric acid at 150–200°, sulphuric acid, phosphoric anhydride, zinc chloride, etc.). Thus, for example, ecgonine, $C_9H_{15}NO_3$, is converted into anhydroecgonine, $C_9H_{13}NO_2$; morphine, $C_{17}H_{19}NO_3$, into apomorphine, $C_{17}H_{17}NO_2$, etc.

A hydroxyl group is frequently eliminated by first substituting for it a halogen atom and then treating the resulting halogen derivative with an alkali. Cinchonine and cinchonidine, $C_{19}H_{21}N_2(OH)$, with phosphorus pentachloride give the isomeric derivatives $C_{19}H_{21}N_2Cl$, which on further treatment with alcoholic potash are converted into cinchene; quinine and quinidine, $C_{20}H_{24}N_2O_2$, in a similar manner give rise to quinene, $C_{20}H_{22}N_2O$.

Conhydrine, $C_8H_{16}N(OH)$, with hydriodic acid gives the iodide $C_8H_{16}NI$, which is converted by alkalies into ε-coniceïne, $C_8H_{15}N$.

2. The oxygen of the alkaloid may occur in a methoxyl group, OCH_3 (neither the ethoxyl, OC_2H_5, nor any other homologous group has as yet been met in a natural alkaloid). At a temperature of about 150°, hydrochloric, or hydriodic acid, will act upon such a derivative, eliminating the methyl as methyl chloride, or iodide, and forming a hydroxyl derivative, which contains just as many hydroxyl as the original substance possessed methoxyl groups.

Zeisel[1] has developed a general method for determining the

[1] Zeisel, M. 6, 989.

methoxyl groups in organic compounds, which is based on this reaction. The method consists in boiling the substance (0.2–0.3 g.) with hydriodic acid of specific gravity 1.68 (10 c.cm.) and passing the methyl iodide thus formed into a receiver containing a solution of silver nitrate. The methyl iodide is hereby decomposed with the formation of silver iodide. From the weight of the latter the number of methoxyl groups is determined, since one molecule of silver iodide corresponds with one methoxyl group.

Among other important alkaloids, the methoxyl group is found in the following:

One in quinine, codeïne; two in hydrastine, brucine; three in narcotine; four in papaverine, aconitine; and six in pseudaconitine.

A group containing oxygen which is met with among a number of the alkaloids is the diatomic one, $CH_2\langle{}^{O-}_{O-}$ (compare piperine, narcotine, narceïne, hydrastine, and berberine).

3. Oxygen is found further in the molecule of the alkaloids in the form of the *carbonyl* group, CO, as ketonic oxygen. The occurrence of this group is, however, rare. It has been shown to be present, indeed, in only three alkaloids, pseudopelletierine, hygrine, and narceïne. These bases form both oximes and hydrazones.

A carbonyl between two nitrogen atoms, $=N-CO-N=$, is characteristic of the alkaloids of the xanthine group (caffeïne, theobromine, etc.), which in their constitution are closely related to uric acid.

4. A certain number of the alkaloids are acid in character, and have a part, or all of their oxygen, in the form of *carboxyl* oxygen, COOH. This group is recognized by the ability, which it gives to the substance containing it, to form an ester with alcohol in the presence of a mineral acid.

Thus benzoylecgonine, narceïne, citrazinic acid, and all the derivatives of asparagine contain the carboxyl group.

Often the acid and basic groups in the same molecule mutually

compensate each other in the free base and derivatives of the *betaïne* type are formed (betaïne, trigonelline, arecaïdine, etc.) Sometimes, from the interaction of an acid radical and a hydroxyl group, *lactones* are formed (narcotine, hydrastine).

5. Lastly a large number of the alkaloids are *esters* and contain the group R—CO—O—R′. These can readily be decomposed by hydrolysis into the acid and the alcohol. The saponifying agents usually employed are water at 100–150°, the mineral acids, baryta-water, and the caustic alkalies. In this way, for example, atropine is decomposed into tropic acid and tropine; cocaïne into benzoic acid, ecgonine, and methyl alcohol.

In certain cases the non-acid product of the saponification is a sugar; solanine is, for example, a nitrogenous glucoside.

Nitrogen.—The natural alkaloids contain in the molecule one or two atoms of nitrogen, rarely three; only the bases of the xanthine group possess a higher number (four or five).

A certain number of the plant bases whose molecules contain several nitrogen atoms are, nevertheless, monacid bases, i.e., they can unite with only one molecule of a monobasic acid. Such, for example, is the case with strychnine, brucine, and the most of the alkaloids of the xanthine group.

The general reactions of organic bases with alkyl iodides, acid anhydrides, nitrous acid, etc., indicate also, in the case of the alkaloids, to what class a base belongs.

Primary bases have been observed as yet only in the asparagine group and in the case of adenine, a derivative of xanthine. Only a few secondary bases are known (conine, anhydrine, chrysanthemine, carpaïne, guvacine, ephedrine, pseudephedrine). By far the greater number of the alkaloids are tertiary bases. In some instances, lastly, the nitrogen functionates as a pentavalent element. The derivatives here fall either into the class of the betaines (betaïne, trigonelline, pilocarpine) or into that of the ammonium hydroxides (choline group).

The nitrogen atom is tightly bound in the molecule of the alkaloid and is removed only with difficulty by simple reactions at the ordinary temperature.

With the primary bases, however, it is quite different, since by the action of nitrous acid the nitrogen is eliminated as such and the base is converted into the corresponding hydroxyl derivative.

It may also be mentioned here, as an example of the ease with which nitrogen is in some cases split off, that certain alkaloids of the ammonium type (choline, pilocarpine) are decomposed by boiling water into hydroxyl derivatives (glycol, pyridine-lactic acid) and trimethylamine.

The cases indicated, however, are exceptional ones and relate only to alkaloids of certain structures. In general the plant bases are characterized by the firmness with which the nitrogen atom is bound to the remainder of the molecular complex. This is to be explained by the fact that the nitrogen atom in the alkaloids does not stand in an open chain, but in connection with several carbon atoms forms a closed chain, or ring. Consequently, in the elimination of the nitrogen the entire molecule at the same time suffers decomposition; but this can only be brought about by violent reactions, such as distillation over zinc-dust or lime, melting with caustic potash, the action of powerful oxidizing agents, or sometimes strong heating with the halogen acids.

These deep-seated decompositions of the molecule often afford valuable indications regarding its structure. In particular they enable us to determine the nature and the number of the alkyl groups attached to the nitrogen. Thus several alkaloids yield methylamine when they are heated with caustic potash or distilled with lime; others under the same conditions give dimethylamine. From these results we naturally conclude that the former contain the group $N-CH_3$ and the latter the group $N(CH_3)_2$. Still other alkaloids afford trimethylamine; these accordingly belong to the group of the quaternary ammonium bases.

In the decomposition of the natural alkaloids, no amines other than those just mentioned have ever been obtained. Consequently methyl is apparently the only alcoholic radical which occurs attached to the nitrogen in these bodies.

Many alkaloids, as citrazinic acid, conine, papaverine, etc., yield only ammonia when they are treated with caustic potash or strong oxidizing agents. These bases accordingly have no alkyl group attached to the nitrogen.

Methyl groups bound to the nitrogen are eliminated as methyl iodide and are replaced by an equal number of hydrogen atoms, when the hydriodic acid salt of the base is subjected to dry distillation.

From this reaction Herzig and Meyer[2] have worked out a method for determining the methyl groups which is analogous to that of Zeisel for determining methoxyl groups. The hydriodide of the base is heated either alone or with ammonium iodide, and a small amount of hydriodic acid, and the methyl iodide evolved is led into a solution of silver nitrate.

In this way there have been found three methyl groups in chrysanthemine and caffeïne; two in cuscohygrine, narceïne, and theobromine; one in trigonelline, arecoline, methylconine, nicotine, hygrine, pseudopelletierine, atropine, cocaïne, morphine, codeïne, narcotine, and eserine; and none in lupinine, lupanine, cinchonine, and harmaline.

It was shown above that it is difficult to eliminate the nitrogen atom from the molecule of an alkaloid, since in general this atom forms a constituent part of the ring. The stability of this ring, at least of the pyridine ring, which is so frequently met, continues only as long as the nitrogen retains its trivalent condition. If, however, the five affinities of the atom are satisfied, for example, by the addition of an alkyl iodide, a salt of a quaternary base being thus formed, the stability of the ring is greatly decreased. An instance of this has already been noted in the oxidation of quinoline.

Hofmann has made use of this peculiarity to eliminate the nitrogen from a cyclic derivative. His method consists in subjecting the hydroxide of the quaternary base to the action of heat or of alkalies. By successively forming and decomposing

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[2] Herzig and Meyer, B. **27**, 319; M. **15**, 613; **16**, 599.

these quaternary bases, the nitrogen is generally finally eliminated as a tertiary amine and there is left an unsaturated hydrocarbon the study of whose constitution has often thrown light on the constitution of the original base. The mechanism of this reaction has already been discussed in studying the decomposition of piperidine (page 28).

This process of Hofmann has been employed with advantage in the case of a number of the natural alkaloids or their derivatives, as conine, tropine, tropic acid, anhydroecgonine, pseudopelletierine, cinchonine, codeïne, thebaïne, cotarnine, hydrastinine, cytisine, and cholchicine.

Reduction.—Many of the alkaloids are unsaturated bodies and are consequently easily acted on by reducing agents, such as sodium amalgam, sodium and alcohol, hydriodic acid, tin and hydrochloric acid, zinc and hydrochloric acid, etc. In this way α-coniceïne, $C_8H_{15}N$, is converted into conine, $C_8H_{17}N$; hydrastinine, $C_{11}H_{11}NO_2$, into hydrohydrastinine, $C_{11}H_{13}NO_2$; papaverine, $C_{20}H_{21}NO_4$, into tetrahydropapaverine, $C_{20}H_{25}NO_4$; cinchonine, quinine, and their isomers into di- and tetrahydrogen derivatives.

Not infrequently the reducing action produces a decomposition of the molecule, the nitrogen being eliminated as ammonia or as methylamine. Thus when tropidine and conine are heated strongly with hydriodic acid, the former gives a heptane, the latter normal octane. In a similar way on reduction with tin and hydrochloric acid, citrazinic acid forms tricarballylic acid.

The alkaloids which can add hydrogen just as readily unite with the halogens, the hydrogen halides, hypochlorous acid, etc.

Oxidation—Of all the reactions to which the alkaloids have been subjected those of oxidation have afforded the most valuable data for the determination of constitution.

The activity of the different oxidizing agents is quite variable, so that it is often possible so to choose these agents as to obtain from the same alkaloid a series of products representing different degrees of oxidation.

A weak oxidizing action is shown by potassium ferricyanide

in alkaline solution, iodine in alcohol, hydrogen peroxide, "chloride of lime," oxygen of the air, ozone, and the salts of gold, silver, mercury, platinum, and iron.

These either tend simply to remove from the alkaloid a part of its hydrogen, as in the conversion of nicotine, $C_{10}H_{14}N_2$, to nicotyrine, $C_{10}H_{10}N_2$; morphine, $C_{17}H_{19}NO_3$, to pseudomorphine, $(C_{17}H_{18}NO_3)_2$; and harmaline, $C_{13}H_{14}N_2O$, to harmine, $C_{13}H_{12}N_2O$; or they cause an addition of one or more atoms of oxygen, as in the oxidation of strychnine, $C_{21}H_{22}N_2O_2$, to oxystrychnine, $C_{21}H_{22}N_2O_3$; nicotine, $C_{10}H_{14}N_2$, to oxynicotine, $C_{10}H_{14}N_2O$.

These products of mild oxidation are often found to be identical with other alkaloids occurring in the plant.

By stronger oxidation an atom of carbon is expelled from the molecule of some alkaloids in the form of carbon dioxide or formaldehyde. Thus with potassium permanganate in alkaline solution, tropine, pseudotropine, scopoline, methylgranatoline, and ecgonine lose a methyl group attached to nitrogen and are converted into secondary bases. So with permanganate in sulphuric acid solution, the cinchona alkaloids yield weak monobasic acids by the oxidation of the group $—CH{=}CH_2$ to carboxyl.

By still more energetic oxidation, as when the oxidizing agents are chromic acid, nitric acid, or manganese dioxide and sulphuric acid, a larger number of carbon atoms are oxidized away, giving rise to formic, acetic, oxalic, or carbonic acids; other carbon complexes are not separated from the molecule, but are changed to carboxyl groups and remain attached either to the aromatic or the nitrogenous nucleus, the most stable parts of the molecule. There are thus obtained the mono- and poly-carboxylic acids of benzol, pyridine, quinoline, isoquinoline, and pyrrolidine.

Several alkaloids such as cytisine, veratrine, aconitine, and emetine are completely destroyed by oxidizing agents. There is then a veritable combustion, the products of which are ammonia, methylamine, carbon dioxide, and oxalic acid.

Action of Alkalies at a High Temperature.—By fusion with caustic alkalies, or by distillation over lime, soda-lime, or baryta, the most of the alkaloids suffer a deep-seated decomposition,

which often affords valuable indications regarding the constitution of these natural bases. Here as in the case of oxidation the less resistant parts of the molecule, the side-chains, are affected and only the stable complexes, as the pyridine and aromatic rings, remain intact. Consequently the end-products of the reaction are comparatively simple derivatives, which in many cases are to be regarded as mother-substances of the alkaloids in question.

It is necessary, however, to avoid drawing too hasty conclusions from this mode of decomposition, since the high temperatures required for the reaction may give rise to such condensation-products as are formed in pyrogenetic processes. Accordingly the results obtained are always to be critically compared with those secured from other modes of decomposition. Such a comparison is further essential since the action of the caustic alkali may cause the nitrogen to be driven out as ammonia, and the complex remaining would then easily undergo condensation at the high temperature.

Distillation with Zinc-dust.—The distillation of the alkaloids over zinc-dust frequently gives rise to the same products of decomposition as are formed by fusion with caustic alkalies.

In general, however, the action takes one of the two following directions:

In the case of alkaloids containing oxygen the zinc plays its customary rôle as a reducing agent and the oxygen is removed.

Alkaloids free from oxygen experience, on the contrary, an oxidation, a certain number of hydrogen atoms being eliminated. This latter reaction undoubtedly depends on the fact that zinc-dust ordinarily contains large quantities of zinc oxide.

Classification of the Alkaloids.—As we indicated in the introduction, the alkaloids, in the sense in which we have used this word, are far from forming a homogeneous and well-defined class of compounds. What we know concerning the constitution of some of them would place these in different series of organic chemistry, but for the greater part the data necessary for a rational classification are wanting. All that can be done in a study such

as this is to arrange the alkaloids in a small number of groups, which are based on similarities in constitution or, where this is necessary, on the common origin of those within a group.

In the scheme which follows the alkaloids are classified largely according to their likeness in constitution, but it has not been deemed advisable to separate alkaloids occurring in the same plant, even though the constitutional differences are great.

1. Alkaloids derived from pyridine (alkaloids of the hemlock, piperine, trigonelline, alkaloids of the betel-nut palm, citrazinic acid, the tobacco alkaloids, the jaborandi alkaloids, cytisine, sparteïne, the lupine alkaloids).

2. Alkaloids derived from pyrrolidine (the solanum alkaloids, the coca alkaloids, the alkaloids of the pomegranate-tree).

3. Alkaloids derived from quinoline (the cinchona alkaloids).

4. Alkaloids derived from isoquinoline (the opium alkaloids, alkaloids from *Hydrastis canadensis* and from *Corydalis cava*).

5. Alkaloids which probably contain the pyridine nucleus, but in a condition of condensation as yet unknown (the strychnos alkaloids, alkaloids of *Peganum harmala*, alkaloids of the aconite group, the veratrum alkaloids).

6. Alkaloids which contain no pyridine nucleus (colchicine, the xanthine group, allantoïn, the asparagine group, the choline group, the alkaloids of mustard-seed, trimethylamine).

7. Alkaloids of unknown constitution.

CHAPTER XI.

ALKALOIDS OF THE HEMLOCK.

THE hemlock (*Conium maculatum L.*, family of the Umbelliferæ) contains three principal alkaloids:

Conine, $C_8H_{17}N$,

γ-Coniceïne, $C_8H_{15}N$,

Conhydrine, $C_8H_{17}NO$.

In smaller quantities there are also found the bases:

Pseudoconhydrine, $C_8H_{17}NO$,

Methylconine, $C_9H_{19}N$.

These alkaloids in the plant are in combination with malic and caffeic acids.[1]

They are found in all parts of the plant, but particularly in the fruit before it has fully ripened. This latter contains according to Wertheim[2] about 1 per cent. conine and 0.01 per cent. conhydrine. From the fresh leaves Dragendorff obtained only about 0.09 per cent. conine, and from the ripe, dry seed Geiger[3] secured about 0.7 per cent.

1. CONINE.

Conine was noticed as early as 1827 by Giesecke[4] as the active principle in the hemlock, and was separated by him as an impure sulphate. Geiger[3] in 1831 first isolated the free base and recognized its alkaloid character. Liebig[5] assigned to it

[1] Hofmann, B. **17**, 1922.
[2] Wertheim, A. **100**, 328.
[3] Geiger, *Magazin für Pharmacie*, **35**, 72, 259.
[4] Giesecke, A. Pharm. [1] **20**, 97.
[5] Liebig, *Magazin für Pharmacie*, **36**, 159.

the formula $C_6H_{14}NO$, but it is probable that the substance which he analyzed was impure or imperfectly dried, since all later investigations have shown that conine does not contain oxygen.

The formula $C_8H_{15}N$ proposed later by Gerhardt[6] was accepted until 1881. At this time Hofmann[7] began a series of investigations which have afforded us the principal data regarding the constitution of the base, and in the course of which he showed that it possessed two more hydrogen atoms than the generally accepted formula indicated. The composition of conine is accordingly $C_8H_{17}N$.

Conine is an oily, colorless liquid, of specific gravity 0.845 at 20°; it distils without decomposition at 166° under a pressure of one atmosphere. It is rather difficultly soluble in cold water (about 1 part in 100) and still less soluble in hot water, so that a cold, saturated solution becomes turbid on being warmed. It dissolves in about six parts of ether, and in alcohol in all proportions. All its solutions are dextrorotatory. It is burning to the taste and it acts as a violent poison; in the pure condition its odor is penetrating, but not disagreeable. The alkaloid is a strong base and precipitates the most of the metals from their salt solutions.

Conine is the first alkaloid that was synthesized, and this eminent result we owe to Ladenburg.[8] The constitution of the base had, however, already been well established by the important work of Hofmann. An observation made by the latter investigator in 1884 proved of the highest value in directing the course of his investigation. On distilling conine hydrochloride over zinc-dust he unexpectedly obtained a large quantity of hydrogen and a base of the formula $C_8H_{11}N$, to which he gave the name of *conyrine* (page 40):

[6] Gerhardt, C. r. 1849, 373.

[7] Hofmann, B. **14**, 705; **15**, 2313; **16**, 558; **17**, 825; **18**, 5, 109.

[8] Ladenburg, B. **14**, 2409; **17**, 1676; **18**, 1587; **19**, 439, 2578; **22**, 1403, 2583; **26**, 854; **27**, 3062; **28**, 163, 1991; A. **247**, 1; **279**, 344.

$$\underset{\text{Conine}}{C_8H_{17}N} \rightarrow \underset{\text{Conyrine}}{C_8H_{11}N} + 3H_2.$$

Zinc chloride was found to produce the same result as zinc-dust.

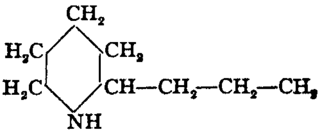
According to a later observation of Tafel,[9] conine is also converted into conyrine when it is heated to 180° with silver acetate in a solution of glacial acetic acid.

These experiments show that conine is the hexa-hydrogen derivative of conyrine; between the two bases exists the same relation as that between piperidine and pyridine. Indeed, Hofmann apparently succeeded in reconverting conyrine into conine by heating the base with concentrated hydriodic acid to 280–300°. The base thus obtained possessed the same composition as conine and appeared to differ in no way from the natural alkaloid. Later, however, Ladenburg showed that the synthesized conine was optically inactive; it accordingly constitutes the optically inactive modification of the natural product.

The formula of conyrine is that of a homologue of pyridine (collidine). By oxidation Hofmann converted it into picolinic acid. Since this is a monobasic acid, conyrine itself can have only *one* side-chain; it must accordingly be either α-propylpyridine or α-isopropylpyridine.

Now this latter base has been synthesized by Ladenburg (page 41), and it is not identical with conyrine. Furthermore, according to an observation of Hofmann there results from the action of hydriodic acid on conine at 300° normal octane, a product which could not have been formed if conine contained an isopropyl group.

Conyrine must accordingly be α-propylpyridine, and conine the dextrorotatory modification of α-propylpiperidine:

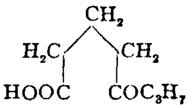


Conine

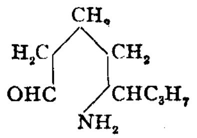
[9] Tafel, B. 25, 1619.

According to the above formula conine is a secondary base, one of the few representatives of this class among the alkaloids. All its reactions, indeed, indicate the presence of the imide group in the molecule. Acetic anhydride, benzoyl chloride in the presence of an alkali, form with it the acetyl and benzoyl derivatives respectively; with methyl iodide or potassium methyl sulphate it gives methylconine, a tertiary base;[10] nitrous acid produces a nitroso-derivative, chlorcarbonic ester a urethane; sodium hypobromite and "chloride of lime" convert it respectively into brom- and chlor-conine,[11] in which the halogen atom is attached to the nitrogen.

Oxidation of Conine.—Conine is easily oxidized. Under the action of bromine-water, platinum chloride, nitric acid, or chromic acid it yields ammonia and normal butyric acid.[12] Wischnegradsky[13] states that under these conditions he obtained a monocarboxylic acid of pyridine, but the observation has not been confirmed. Later Wolffenstein[14] oxidized conine with hydrogen peroxide and secured from it a coniceïne, $C_8H_{15}N$ (page 135), acetic acid, *butyrylbutyric acid*,



and *amido-propylvaleraldehyde*,

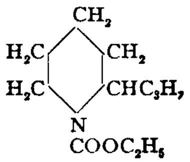


This last derivative is reconverted into conine by the action of zinc and hydrochloric acid, while on treatment with solid

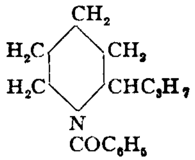
[10] Passon, B. **24**, 1678.
[11] Lellmann, B. **22**, 1000.
[12] Blyth, A. **70**, 73. Grünzweig, A. **162**, 217; **168**, 118.
[13] Wischnegradsky, B. **13**, 2316.
[14] Wolffenstein, B. **28**, 1459.

alkalies it gives rise to a mixture of conine and coniceïne. By oxidation, accordingly, the pyridine ring is opened between the nitrogen and one of the neighboring carbon atoms, and the open chain thus formed is again closed by the action of reducing or dehydrating agents. These reactions are strictly comparable with those which have already been discussed in the case of piperidine (page 27).

Similar results which show the easy rupture of the conine ring by oxidizing agents have been obtained by Schotten and Baum [15] in the oxidation of two derivatives of conine, *conylurethane*,



and *benzoylconine*,



Conylene.—Wertheim [16] observed in 1862 that by the action of nitrous acid conine is converted into a yellow oil of the formula $C_8H_{16}N_2O$, which is difficultly soluble in water, acids, and alkalies, and which boils at 150–160°. Since at that time $C_8H_{15}N$ was regarded as the formula for conine, the close relation between this alkaloid and the body $C_8H_{16}N_2O$ escaped the attention of Wertheim. He, indeed, considered the latter to be a derivative of conhydrine, $C_8H_{17}NO$, and named it consequently *azoconhydrine*. It is, however, nothing other than nitrosoconine, $C_8H_{16}N—NO$. It gives the characteristic reactions of a nitros-

[15] Schotten and Baum, B. **15**, 1947; **16**, 643; **17**, 2548; **19**, 500.
[16] Wertheim, A. **123**, 157; **130**, 269.

amine; on treatment with an ethereal solution of hydrogen chloride, or on reduction with zinc and hydrochloric acid, it is reconverted into conine.

Wertheim observed, further, an interesting decomposition of nitrosoconine produced by the action of phosphoric anhydride. When these two substances are heated together to 80–90° the nitrogen is eliminated and there is formed a hydrocarbon of the formula C_8H_{14}, *conylene:*

$$\underset{\text{Nitrosoconine}}{C_8H_{16}N_2O} \rightarrow \underset{\text{Conylene}}{C_8H_{14}}+N_2+H_2O.$$

Conylene is a colorless liquid which boils at 126°. As an unsaturated body, it forms an addition-product with bromine; it is insoluble in water and has no poisonous properties.

The same hydrocarbon is also produced by the decomposition of conine according to the method of Hofmann (pages 29, 122). As a secondary base conine can react with two molecules of methyl iodide.

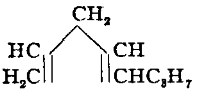
The product thus formed, the *methyl iodide of methylconine,* yields with moist silver oxide a hydroxide which on dry distillation loses water and forms a new tertiary base, *dimethylconine* (a dextrorotatory liquid, boiling-point 182°):

$$\underset{\text{Methyl hydroxide of methylconine}}{C_8H_{16}{=}N\begin{matrix}\diagup CH_3\\ -OH\\ \diagdown CH_3\end{matrix}} \rightarrow \underset{\text{Dimethylconine}}{C_8H_{15}{-}N\begin{matrix}\diagup CH_3\\ \\ \diagdown CH_3\end{matrix}} + H_2O.$$

If now the dimethylconine is subjected to the same treatment as the preceding, i.e., its methyl hydroxide is formed and heated, there results a second decomposition into trimethylamine and conylene:

$$\underset{\text{Methyl hydroxide of dimethylconine}}{C_8H_{15}{-}N\begin{matrix}\diagup CH_3\\ -CH_3\\ -CH_3\\ \diagdown OH\end{matrix}} \rightarrow \underset{\text{Conylene}}{C_8H_{14}} + \underset{\text{Trimethylamine}}{N\begin{matrix}\diagup CH_3\\ -CH_3\\ \diagdown CH_3\end{matrix}} + H_2O.$$

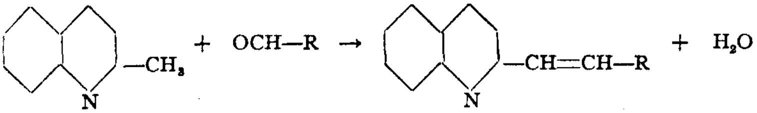
As we see, all these reactions are completely analogous to those which piperidine gives under the same treatment. Conylene must accordingly be regarded as a ***propylpiperylene:***



Synthesis of Conine.—The comparatively simple composition of conine early incited a number[17] of investigators to attempt the synthesis of the alkaloid. It was not until 1886, however, that Ladenburg[18] succeeded in effecting the synthesis.

This investigator sought first to prepare α-propylpyridine and then to change this by reduction into α-propylpiperidine. He wished to use for this purpose the process which he had already employed in obtaining a number of the α-substitution-products of pyridine and which consisted in heating to 300° the addition-products of this base with the alkyl iodides. We have already seen (page 41) that this process does not in this particular case give the desired result, since the propyl group at the temperature required undergoes rearrangement to the isopropyl group. There is consequently formed a mixture of α- and γ-isopropylpyridine.

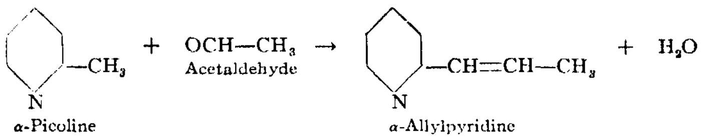
Since this general method of preparation could not be employed in the synthesis of conine, Ladenburg sought another way to attain this end. He applied successfully to pyridine derivatives a reaction which Jacobsen and Reimer had used in the quinoline series (p. 92). As these investigators show, quinaldine (α-methyl-quinoline) reacts with aldehydes so that two atoms of hydrogen from the group CH_3 are eliminated with the oxygen of the aldehyde group as water and there is thus formed a derivative with an unsaturated side-chain:



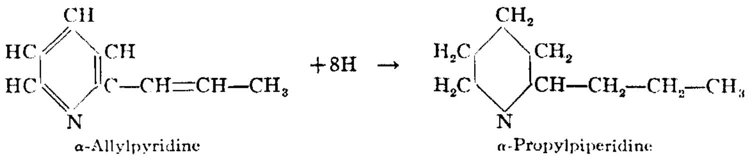
[17] Schiff, A. **157**, 352; **166**, 88. Michael and Grundelach, Am. Chem. Jour., **2**, 172.

[18] Ladenburg, B. **19**, 439, 2578; **22**, 1403; **27**, 3062; **28**, 163, 1991; **30**, 485.

In the same way Ladenburg succeeded in condensing α-picoline (α-methylpyridine) with acetaldehyde to *allylpyridine:*



By reduction the allylpyridine was converted into *α-propyl-piperidine:*



The actual carrying out of the synthesis was, however, somewhat troublesome. Paraldehyde condenses with α-picoline only at a temperature above 250°, and even then the reaction is incomplete. From 380 g. of α-picoline were obtained only 45 g. of allylpyridine. This is a liquid which boils at 188–192°; its constitution follows from its conversion by oxidation into picolinic acid.

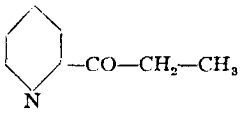
The base obtained by the reduction of the allylpyridine with sodium and alcohol must be α-propylpiperidine. It showed the closest resemblance to the natural conine. Its odor, its specific gravity, its boiling-point, its physiological properties were exactly the same. On distillation with zinc-dust, there was formed a body which was fully identified with conyrine. In one point, however, the synthesized base differed from the natural alkaloid. It was optically inactive. This inactivity was undoubtedly due to the formation of the racemic modification of conine—a result which was indeed to be expected, since in such a synthesis there is equal possibility of the production of dextro- and lævo-forms.

This explanation of the inactivity was verified by Ladenburg

in the separation of the two forms by the fractional crystallization of their bitartrates. To a saturated solution of the inactive propylpiperidine bitartrate was added a crystal of the natural bitartrate. The crystalline precipitate which gradually formed was carefully freed from the mother-liquor. These crystals were the bitartrate of dextro-α-propylpiperidine. The base obtained from them by treatment with an alkali was in all its chemical, physical, and physiological properties exactly identical with the natural conine.

From the mother-liquor Ladenburg obtained a conine which differed from the natural product only in its optical activity; this was the hitherto unknown lævo-conine.

In 1891 Engler and Bauer [19] effected a second synthesis of conine in the following way: An equimolecular mixture of the calcium salts of propionic and picolinic acids, when subjected to dry distillation, forms *α-ethyl pyridyl ketone:*



On reduction with sodium and alcohol this is converted into α-ethyl piperidyl alcamine (page 54) and optically inactive α-propylpiperidine, which can be separated into its active forms by fractional crystallization of the bitartrate.

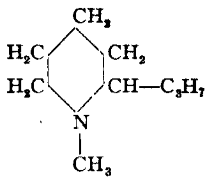
More recently Ladenburg [20] states that on distilling conine hydrochloride over zinc-dust he obtained a base stereoisomeric with dextro-conine, the so-called isoconine, whose occurrence is considered as due to the asymmetry of the nitrogen atom. This isoconine is, however, only a mixture of inactive conine with dextro-conine.[21]

[19] Engler and Bauer, B. **24**, 2530; **27**, 1775.
[20] Ladenburg, B. **26**, 854; **27**, 853, 859; **29**, 2706; **34**, 3416.
[21] Wolffenstein, B. **27**, 2615; **29**, 1956.

2. METHYLCONINE.

This alkaloid, which Kekulé and von Planta[22] mention as early as 1854, was first prepared in the pure condition by Wolffenstein[23] in 1894 from the alkaloids of the hemlock. It is a colorless, lævorotatory liquid, of specific gravity 0.8318 at 24° and of boiling-point 173–174°.

It possesses the constitution



It is thus a nitrogen-methylated conine and may accordingly be prepared by heating conine with an aqueous solution of methyl potassium sulphate to 100°.[24]

3. CONICEÏNES.

Between conyrine, $C_8H_{11}N$, and conine, $C_8H_{17}N$, we should according to the theory expect intermediate products of the formulæ $C_8H_{13}N$ and $C_8H_{15}N$. These derivatives may occur in several isomeric forms in which some will be tertiary, others secondary bases. No derivative of the composition $C_8H_{13}N$ is as yet known; on the other hand, there are five isomers of the formula $C_8H_{15}N$ whose preparation we owe to Hofmann and Lellmann.[25]

These so-called *coniceïnes* (tetrahydroconyrines or α-propylpiperideïnes) have been synthesized in part from conine, in part from conhydrine.

[22] Kekule and von Planta, A. 89, 120.
[23] Wolffenstein, B. 27, 2611.
[24] Passon, B. 24, 1678.
[25] Hofmann, B. 18, 5, 109; 16, 558. Lellmann, B. 22, 1000; 23, 680, 2141; A. 259, 193.

α-Coniceïne.—This was obtained by Hofmann by heating conhydrine with concentrated hydrochloric acid to 220°:

$$\underset{\text{Conhydrine}}{C_8H_{17}NO} \rightarrow \underset{\alpha\text{-Coniceïne}}{C_8H_{15}N} + H_2O.$$

It is a liquid which boils at 158° and is little soluble in water; it is a tertiary base and is more poisonous than conine. It is not reduced by sodium amalgam, but hydriodic acid at a high temperature (220°) converts it into conine.

The behavior of α-coniceïne has been insufficiently studied to establish its constitution.

It is not impossible that it may be a stereoisomer of δ- and ε-coniceïne (see below).

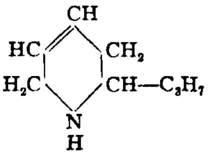
β-Coniceïne.—This was also prepared by Hofmann from conhydrine, in part directly by treating it with phosphoric anhydride, in part by distilling with lime iodoconine which results from the action of hydriodic acid on conhydrine:

$$\underset{\text{Conhydrine}}{C_8H_{17}NO + HI} \rightleftarrows \underset{\text{Iodoconine}}{C_8H_{16}IN} + H_2O.$$

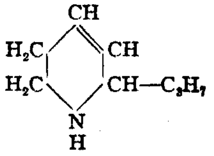
$$\underset{\text{Iodoconine}}{C_8H_{16}IN} \rightarrow \underset{\beta\text{-Coniceïne}}{C_8H_{15}N} + HI.$$

β-Coniceïne is a solid crystallizing in needles which melt at 41°; it boils at 168°. It is little soluble in water, but quite soluble in alcohol and in ether. It acts as a strong, secondary base; its poisonous character is less pronounced than that of conine.

In accordance with our present views concerning the constitution of conhydrine, we may assign to β-coniceïne one of the two following formulæ:



or



γ-Coniceïne.—γ-Coniceïne is formed by the action of alkalies on chlor- or bromconine (page 129):

$$\underset{\text{Chlorconine}}{C_8H_{16}ClN} \rightarrow \underset{\gamma\text{-Coniceïne}}{C_8H_{15}N} + HCl.$$

According to Wolffenstein[26] γ-coniceïne occurs also in the crude conine of commerce.

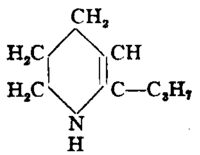
It is a liquid little soluble in water. It boils at 171–172°, possesses a very strong alkaline reaction, and is one of the most active poisons, being about seventeen times more poisonous than conine itself.

γ-Coniceïne is a secondary base, optically inactive. It is easily reduced either by tin and hydrochloric acid or by sodium and alcohol, and is thereby converted into inactive conine. On distillation with zinc-dust, conyrine is formed.

From these various properties its constitution is established.

Its optical inactivity is only explained by the absence of a hydrogen atom from the carbon atom, which in conine is asymmetric. Its ease of reduction indicates the presence of a double bond. This must lie between the asymmetric carbon atom and the neighboring *carbon* atom and not the nitrogen, since γ-coniceïne as a secondary base contains the group NH.

Consequently we have the following formula:



γ-Coniceïne

The above formation of γ-coniceïne from chlorconine must be explained in the same way as the formation of piperideïne

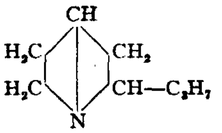
[26] Wolffenstein, B. 28, 302; 29, 1956.

from chlorpiperidine (page 23). Here also we are to assume a migration of the halogen from the nitrogen to the α-carbon atom.

γ-Coniceïne has less tendency to polymerize than piperideïne. This is undoubtedly due to the presence of the propyl group.

δ-**Coniceïne.**—Lellmann obtained this base by treating bromconine with sulphuric acid. It is a tertiary base, of boiling-point 158°, lævorotatory, not reducible by sodium and alcohol.

This last property indicates the absence of a double bond in the molecule of δ-coniceïne. It is quite probable, then, that in its formation the bromine attached to the nitrogen is eliminated with the γ-hydrogen atom and that δ-coniceïne has accordingly the following formula:



ϵ-**Coniceïne.**—This base is formed by the action of alkalies on iodoconine (formed from conhydrine). In its properties it is quite similar to its isomer δ-coniceïne; it is probably stereoisomeric with this base. It boils at 150–151°. It is a tertiary base, dextrorotatory, irreducible by sodium and alcohol.

4. CONHYDRINE.

Conhydrine was discovered by Wertheim[27] in the hemlock in 1856. The alkaloid occurs in the plant in small quantities. It possesses the formula $C_8H_{17}NO$; it crystallizes from ether in colorless leaflets which melt at 118°. It may be sublimed, and distils without decomposition at 225–226°. In odor it resembles conine; in poisonous character it is but slightly less active than this base. It is somewhat soluble in water, easily so in alcohol and ether.

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[27] Wertheim, A. 100, 328.

Like conine, conhydrine is a secondary base and turns the plane of polarization to the right.

The oxygen atom in the alkaloid forms part of a hydroxyl group. When conhydrine is heated with concentrated hydriodic acid to 150°, the hydroxyl is easily replaced by an atom of iodine:

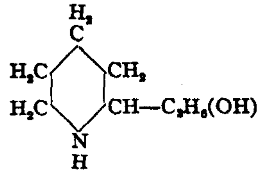
$$C_8H_{16}(OH)N + HI \rightarrow C_8H_{16}IN + H_2O.$$ [28]

The same hydroxyl is eliminated with an atom of hydrogen when conhydrine is treated with dehydrating agents (fuming hydrochloric acid at 220°, phosphoric anhydride, etc.). There is thus formed a mixture of *α*- and *β*-coniceïne:[28, 29]

$$\underset{\text{Conhydrine}}{C_8H_{16}(OH)N} \rightarrow \underset{\text{Coniceïne}}{C_8H_{15}N} + H_2O.$$

The relation existing between conhydrine and conine is shown by the fact that the iodo-derivative mentioned above, $C_8H_{16}IN$, is reduced to conine by tin and hydrochloric acid. Conhydrine is accordingly a hydroxylated conine, and in establishing its constitution it remains only to determine the position of the hydroxyl group.

The hydroxyl cannot be in the side-chain, since the three alcamines theoretically possible and of the formula,



[28] Hofmann, B. 18, 5.

[29] Lellmann, B. 23, 2141; A. 259, 193.

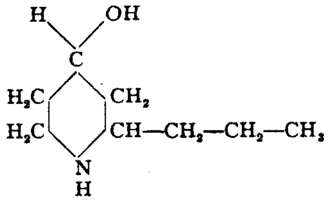
have all been synthesized (page 53) and none of them is identical with conhydrine.

When conhydrine is dehydrated by means of hydrochloric acid, α-coniceïne is formed, and when iodoconine (obtained from conhydrine, page 136) is treated with alkalies, ε-coniceïne is obtained. These two coniceïnes are tertiary bases; in their formation, consequently, the imide hydrogen of the conhydrine is eliminated with the hydroxyl group, or with the iodine atom which replaces the hydroxyl in the iodoconine. Such a reaction, however, can only take place when the hydroxyl or the atom of iodine occupies the α-, α′-, or γ-position.

Now, ε-coniceïne is optically active (lævorotatory); accordingly in iodoconine the iodine atom is not attached to the asymmetric carbon atom, since otherwise on its expulsion the asymmetry would be destroyed.

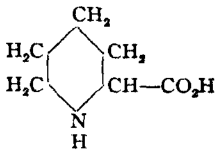
Further, ε-coniceïne cannot be reduced by sodium and alcohol; it, consequently, contains no double bond. For this reason the iodine atom also does not occupy the α′-position, since in this case its elimination with the imide hydrogen would have produced a double bond.

We are thus led to the conclusion that iodoconine is a γ-derivative and that consequently conhydrine possesses the following constitution:



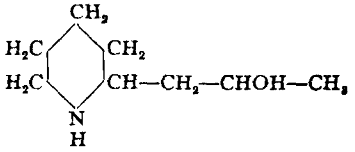
This constitution is disputed by Willstätter.[80] By the oxidation of conhydrine, as also of pseudoconhydrine, with chromic acid, he states that he obtains *l-pipecolinic acid* (melting-point 264–265°):

[80] Willstätter, B. 34, 3166.



l-Pipecolinic acid

This would indicate that the hydroxyl group is in the side-chain. Willstätter considers that conhydrine is probably structurally identical with the *pipecolyl methyl alcamine* of Ladenburg (page 53), since both possess the same boiling-point:



α-Pipecolyl methyl alcamine

5. PSEUDOCONHYDRINE.

This alkaloid was discovered in the hemlock in 1891 by Merck,[31] and has since that time been studied by several investigators.[32] It is isomeric with conhydrine and possesses quite similar properties.

The base forms a crystalline, deliquescent powder, easily soluble in water and in the leading organic solvents. Its melting-point is 101–102°, its boiling-point 229–231°. Like conhydrine it is a secondary, dextrorotatory base.

Pseudoconhydrine is probably a stereoisomer of conhydrine. If the former is converted into its gold salt and this is then decomposed, the original alkaloid is not obtained, but instead of it conhydrine.

Even by warming for a few hours with ligroin, pseudoconhydrine is converted into conhydrine.

[31] Merck, B. **24**, 1671.

[32] Ladenburg and Adam, *ibidem*. Engler and Kronstein, B. **27**, 1779. Engler and Bauer, B. **27**, 1775.

Engler and Kronstein have observed, further, that when pseudoconhydrine is crystallized from different solvents (ligroin, toluol, etc.) it changes to a third form, which is characterized both by its lower melting-point (52–69°) and by its retransformation to the original base when heated.

CHAPTER XII.

PIPERINE.

THE fruits of *Piper nigrum* L. (black and white pepper) and those of *Piper longum* L. (family of the Piperaceæ) contain in addition to a terpene a considerable quantity (5–9%) of an alkaloid called *piperine*. This was isolated by Oersted[1] in 1819. The first analyses made by a large number of chemists gave rather discordant results. The formula $C_{17}H_{19}NO_3$ which Regnault[2] found has, however, been confirmed by all subsequent investigators.

Piperine crystallizes in prisms which melt at 128–129°. It is almost insoluble in cold water, but easily soluble in alcohol and ether. The alcoholic solution has a very sharp taste and is without action on polarized light.

Piperine is a weak base; it does not react alkaline, nor does it dissolve in dilute acids. Only with concentrated mineral acids does it form salts, but even these are readily dissociated by water.

The first observation of importance concerning the constitution of this alkaloid was made by Wertheim and Rochleder[3] in 1848. On distilling piperine with lime, these investigators obtained a volatile base. A little later Anderson[4] and Cahours[5] gave to this base the formula $C_5H_{11}N$ and named it *piperidine*. Some years later von Babo and Keller[6] completed this obser-

[1] Oersted, *Schweigger's Journal für Chemie und Physik*, **29**, 80.
[2] Regnault, A. **24**, 315.
[3] Wertheim and Rochleder, A. **54**, 255; **70**, 58.
[4] Anderson, A. **75**, 82; **84**, 345.
[5] Cahours, A. ch. [3] **38**, 76.
[6] von Babo and Keller, J. pr. **72**, 53.

vation and showed that alcoholic potash decomposes piperine into the base, piperidine, and a monobasic acid which they called *piperic acid:*

$$\underset{\text{Piperine}}{C_{17}H_{19}NO_3} + H_2O \rightarrow \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid}}{C_{12}H_{10}O_4}.$$

This reaction shows that piperine is to be considered as a piperidine in which an atom of hydrogen is replaced by the radical of piperic acid:

$$C_5H_{10}N—CO—C_{11}H_9O_2.$$

We have already discussed the constitution of piperidine (page 25); it remains for us to show how that of piperic acid is established.

Piperic Acid, $C_{12}H_{10}O_4$.—This acid crystallizes from alcohol in needles which melt at 216–217° and may be sublimed with partial decomposition; it is almost insoluble in water, little soluble in alcohol and ether.

The constitution of the acid has been especially studied by Fittig [7] and his students.

Piperic acid is an unsaturated body which in a solution of carbon bisulphide absorbs four atoms of bromine; on reduction it adds four hydrogen atoms and is thus converted into a saturated acid, *hydropiperic acid*, of the formula $C_{12}H_{14}O$.

On oxidation with potassium permanganate piperic acid is converted successively into piperonal, $C_8H_6O_3$, and piperonylic acid, $C_8H_6O_4$.

The study of these two oxidation-products has contributed much to explain the constitution of piperic acid.

Piperonylic Acid is a saturated, monobasic acid. It melts at 228°. With hydrochloric acid at 170°, or water at 210°; it is decomposed into protocatechuic acid and carbon:

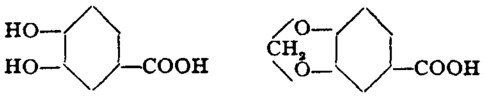
$$\underset{\text{Piperonylic acid}}{C_8H_6O_4} \rightarrow \underset{\text{Protocatechuic acid}}{C_7H_6O_4} + C.$$

[7] Fittig, A. **152**, 35, 56; **159**, 129; **168**, 94; **216**, 171; **227**, 31.

Fittig and Remsen effected the synthesis of piperonylic acid by heating a mixture of protocatechuic acid, potassium hydroxide, and methylene iodide:

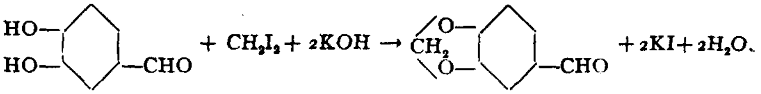
$$C_7H_6O_4 + CH_2I_2 + 2KOH \rightarrow C_8H_6O_4 + 2KI + 2H_2O.$$

This mode of formation makes piperonylic acid the methylene ether of protocatechuic acid:



Protocatechuic acid   Piperonylic acid

Piperonal forms prisms which melt at 37°; it distils at 263° and possesses a very agreeable odor of heliotrope. It is the aldehyde of piperonylic acid; it gives all the characteristic reactions of benzaldehyde; with potassium permanganate it is oxidized to piperonylic acid. Its synthesis was effected by Wegscheider[8] by heating protocatechuic aldehyde in alkaline solution with methylene iodide:



Protocatechuic aldehyde   Piperonal

The reaction is entirely analogous to the formation above of piperonylic acid.

Now piperic acid differs from piperonylic acid by the presence of the additional group C_4H_4. This group can only be introduced in the formula of piperonylic acid between the benzol ring and the carboxyl. If it stood in any other position in the molecule, it would on oxidation give rise to a second carboxyl. The constitution of this group has been established almost beyond doubt by the investigations of Fittig and Weinstein on hydro-

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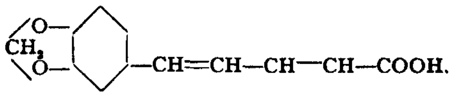
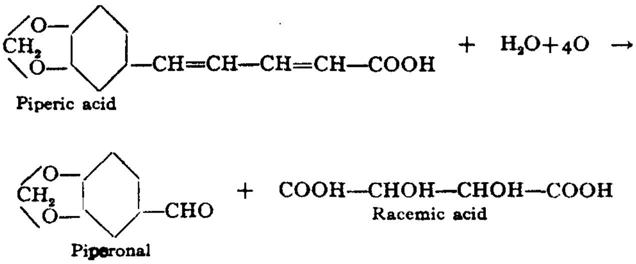
[8] Wegscheider, M. 14, 382.

piperic acid. According to these authors piperic acid bears the formula



The correctness of this formula is further confirmed by an observation of Doebner [9] that piperic acid oxidized with a solution of cold potassium permanganate forms racemic acid and piperonal:



On the basis of the above constitution for piperic acid, Ladenburg and Scholtz [10] in 1894 succeeded in effecting its synthesis. They started with piperonal and caused this to condense with acetaldehyde by the action of dilute soda solution (Claisen's reaction). There was thus first formed *piperonylacroleïn* (yellow leaflets, melting-point 70°):

$$\underset{\text{Piperonal}}{CH_2O_2{=}C_6H_3{-}CHO} + \underset{\text{Acetaldehyde}}{CH_3{-}CHO} \rightarrow$$

$$\underset{\text{Piperonylacroleïn}}{CH_2O_2{=}C_6H_3{-}CH{=}CH{-}CHO} + H_2O.$$

This derivative was now heated with sodium acetate and

[9] Doebner, B. 23, 2375.
[10] Ladenburg and Scholtz, B. 27, 2958.

acetic anhydride (Perkin's reaction). The product of the reaction proved to be identical with piperic acid:

$$CH_2O_2{=}C_6H_3{-}CH{=}CH{-}CHO + CH_3{-}COOH \rightarrow$$
Piperonylacrolein

$$CH_2O_2{=}C_6H_3{-}CH{=}CH{-}CH{=}CH{-}COOH + H_2O.$$
Piperic acid

According to Scholtz[11] piperic acid may also be obtained by the condensation of piperonylacroleïn with malonic acid. There is first formed *piperonylene-malonic* acid:

$$CH_2O_2{=}C_6H_3{-}CH{=}CH{-}CH{=}C(COOH)_2.$$

When this is heated above its melting-point a molecule of carbon dioxide is lost and piperic acid results.

Constitution and Synthesis of Piperine.—The synthesis of piperine from its products of decomposition, piperidine and piperic acid, was effected by Rügheimer[12] as early as 1882, at a time, indeed, when neither piperidine nor piperic acid had been synthesized.

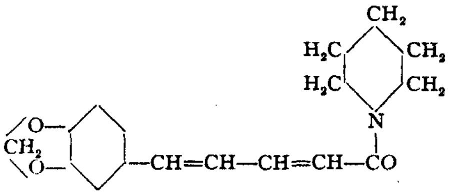
Rügheimer prepared first the chloride of piperic acid by the action of phosphorus pentachloride on the acid and then heated this chloride with piperidine in a benzol solution. Piperine is thus formed with the elimination of hydrogen chloride:

$$C_{11}H_9O_2{-}COCl + C_5H_{11}N \rightarrow (C_5H_{10}N){-}CO{-}C_{11}H_9O_2 + HCl.$$
Piperyl chloride — Piperidine — Piperine

In this reaction, from the nature of piperidine as a secondary base, it is undoubtedly the imide hydrogen atom which has

[11] Scholtz, B. 28, 1187.
[12] Rügheimer, B. 15, 1390.

reacted with the chlorine of the acid chloride. Piperine must accordingly possess the following constitution:



Piperine

Following Rügheimer's synthesis, Scholtz has effected condensation between piperidine and the homologues of piperic acid, thus obtaining the higher homologues of piperine.

CHAPTER XIII.

TRIGONELLINE.

THIS alkaloid was discovered in 1885 by Jahns [1] in the seeds of *Trigonella fœnum græcum* L. (family of the Leguminosæ). It occurs here in quite small quantity (0.13%) together with an essential oil, a bitter substance, and traces of choline. Later Schulze [2] found trigonelline also in flax (*Canabis sativa* L.), in peas (*Pisum sativum* L.), and in oats (*Avena sativa* L.). Thoms [3] has noted its occurrence in the seeds of *Strophantus hispidus* and *Strophantus Kombé* Oliv.

In composition it corresponds with the formula $C_7H_7NO_2$. It crystallizes from alcohol in colorless prisms containing a molecule of water. On being heated, it shows no definite melting-point, but darkens and undergoes decomposition.

Trigonelline is very soluble in water, somewhat less soluble in alcohol, and insoluble in ether. Its solutions react neutral toward litmus. It possesses no marked physiological properties.

Soon after the discovery of trigonelline, Hantzsch [4] undertook the study of the betaïnes of the pyridine carboxylic acids (page 73). He prepared and described among others the methyl betaïnes of picolinic and nicotinic acids. These two derivatives possess the same empirical formula as trigonelline; Hantzsch called attention to the isomerism, but did not study the matter further.

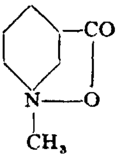
In the following year Jahns,[5] having prepared and purified

[1] Jahns, B. **18**, 2518.
[2] Schulze, B. **27**, 769; **29**, Ref. 34.
[3] Thoms, B. **31**, 271, 408.
[4] Hantzsch, B. **19**, 31.
[5] Jahns, B. **20**, 2840.

a large quantity of trigonelline, continued his study of the base. By the action of barium hydroxide on it he split off methylamine. When trigonelline was heated with concentrated hydrochloric acid to 260–270°, it suffered decomposition into methyl chloride and nicotinic acid:

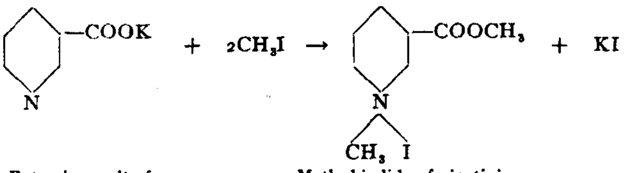
$$C_7H_7NO_2 + HCl \rightarrow CH_3Cl + C_6H_5NO_2.$$

Further comparative study of the base proved beyond doubt its identity with the methyl betaïne of nicotinic acid. The constitution of trigonelline is accordingly expressed by the following formula:

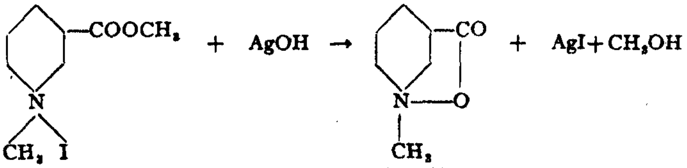


Trigonelline

As we have seen (page 75), trigonelline, according to the experiments of Hantzsch, is formed by heating the potassium salt of nicotinic acid with methyl iodide to 150° and by treating the iodide thus resulting with moist silver oxide:

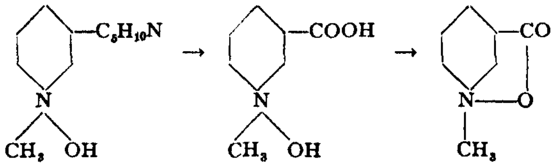


Potassium salt of nicotinic acid — Methyl iodide of nicotinic acid methyl ester



Trigonelline

Pictet and Genequand [6] have converted nicotine into trigonelline in an interesting way by oxidizing a methyl hydroxide of nicotine with potassium permanganate:



Methyl hydroxide of nicotine — Methyl hydroxide of nicotinic acid — Trigonelline

[6] Pictet and Genequand, B. 30, 2117.

CHAPTER XIV.

ALKALOIDS OF THE BETEL-NUT PALM

In 1888–1891 Jahns[1] isolated from areca- or betel-nuts, the fruit of the *Areca catechu* (family of the Palmæ), the following four alkaloids, which together with a small quantity of choline are found in the nuts in combination with tannic acid:

Arecaïdine, $C_7H_{11}NO_2$;
Arecoline, $C_8H_{13}NO_2$;
Guvacine, $C_6H_9NO_2$;
Arecaïne, $C_7H_{11}NO_2$.

1. ARECAÏDINE.

Arecaïdine occurs in small quantities in the betel-nut. The alkaloid crystallizes in plates containing one molecule of water; dehydrated, these melt with decomposition at 223–224°. It is easily soluble in water, difficultly soluble in absolute alcohol, and insoluble in ether, chloroform, and benzol. It is without action on the animal organism.

The alkaloid forms salts with both acids and bases; its aqueous solution reacts weakly acid. The acid character is due to the presence of a carboxyl group, since the alkaloid is converted into its ester by the action of alcohol and hydrochloric acid.

Arecaïdine possesses a methyl group attached to the nitrogen atom. On treatment with concentrated hydrochloric acid at 240°, methyl chloride is formed; on being heated with lime or

[1] Jahns, B. 21, 3404; 23, 2972; 24, 2615; A. Pharm. 229, 669.

baryta, methylamine is split off. Its formula may accordingly be represented as follows:

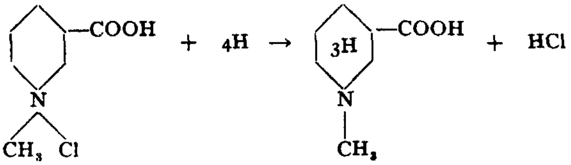
$$CH_3—N=C_6H_7—COOH.$$

Arecaïdine is an unsaturated body. If it is reduced with sodium and alcohol, it adds two atoms of hydrogen and is thereby converted into *dihydroarecaïdine:*

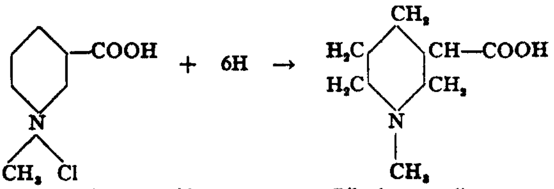
$$CH_3—N=C_6H_9—COOH.$$

This forms hygroscopic crystals which contain one molecule of water and which fuse in the anhydrous condition at 162–163°. It is very soluble in water, alcohol, and chloroform; insoluble in ether; and in reaction is neutral.

The rough formulæ of arecaïdine and its reduction-product cause one to suspect that these substances are carboxylic derivatives of a methylpiperideïne and a methylpiperidine respectively. Such is in fact the case; arecaïdine is *methyltetrahydronicotinic* acid, and dihydroarecaïdine is *methylnipecotinic* acid. This was shown by Jahns in the synthesis of these alkaloids. He obtained them both at one time by reducing with tin and hydrochloric acid the methyl chloride of nicotinic acid:



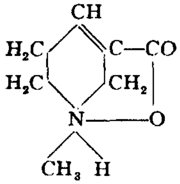
Methyl chloride of nicotinic acid **Arecaïdine**

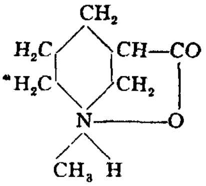


Methyl chloride of nicotinic acid **Dihydroarecaïdine**

The position of the double bond in arecaïdine is as yet undetermined; the optical inactivity of the alkaloid, however, favors the position given in the formula following.[2]

The constitution of the two alkaloids should probably be expressed as follows:


Arecaïdine


Dihydroarecaïdine

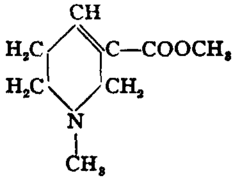
According to this view, they are the tetra- and hexa-hydro-derivatives of trigonelline.

2. ARECOLINE.

Arecoline is the chief alkaloid in the betel-nut. It occurs there in quantity nearly equal to that of the three other bases taken together, or about 0.1 per cent. It is an oily liquid, inodorous and colorless, volatile with steam, and boiling at 209°. It is soluble in all proportions in water, alcohol, ether, and chloroform. Its reaction is strongly alkaline.

Alone among the alkaloids of the betel-nut, arecoline possesses pronounced physiological activity. It is to this alkaloid, indeed, that the betel-nut owes its anthelminthic action.

Arecoline is the methyl ester of arecaïdine:



On being heated with acids or bases, arecoline is saponified

[2] Meyer, M. 23, 22.

with the formation of arecaïdine. Conversely, by treating arecaïdine with methyl alcohol and hydrochloric acid, arecoline is formed.

If the methyl alcohol is replaced by ethyl alcohol, the corresponding ester, *homarecoline*, $C_9H_{15}NO_2$, is obtained. This is a liquid quite similar in its physical and physiological properties to arecoline.

Arecoline forms with methyl iodide a well-defined crystalline addition-product (the methiodide).[3]

3. Guvacine.

This alkaloid, which receives its name from the old Indian designation of the betel-nut palm, "guvaca," crystallizes from alcohol in shining crystals, which melt with decomposition at 271–272°. It is insoluble in alcohol, ether, chloroform, and benzol, easily soluble in water, acids, and alkalies. Its reaction is neutral.

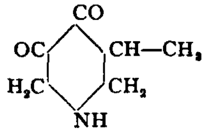
The constitution of guvacine has not been definitely established as has that of arecaïdine and arecoline.

It contains apparently no carboxyl group, since it cannot be converted into an ester with alcohol in the presence of hydrochloric acid.

It forms a nitrosamine on treatment with nitrous acid; heated with sodium acetate and acetic anhydride, it is converted into an acetyl derivative. These facts indicate that it is a secondary base.

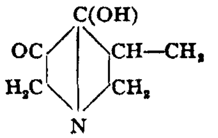
On distilling guvacine over zinc-dust, Jahns obtained a pyridine base of the formula C_6H_7N, which he believed to be β-picoline. When the alkaloid was heated with barium hydroxide, ammonia was given off.

From these reactions Jahns assigned to guvacine the constitution



[3] Willstätter B. 30, 729.

or the tautomeric form



In favor of these tautomeric forms it may be noted that guvacine shows the reactions of a phenol, and also that two isomeric methyl derivatives may be obtained.

Further data, however, will be required to confirm these formulæ.

4. Arecaïne.

Arecaïne crystallizes with one molecule of water. The crystals lose their water at 100° and melt with decomposition at 213–214°. The alkaloid is easily soluble in water, but little soluble in absolute alcohol, and insoluble in ether, chloroform, and benzol. In reaction it is neutral.

Arecaïne is *n*-methylguvacine and is consequently a tertiary base. Jahns obtained the base by treating guvacine, dissolved in methyl alcohol, with sodium and subsequently heating the product to 140–150° with potassium methyl sulphate.

CHAPTER XV.

CITRAZINIC ACID.

THIS substance, which bears the formula $C_6H_5NO_4$, was extracted by von Lippmann [1] in 1893 from beet-root (*Beta vulgaris* L., family of the Chenopodiaceæ).

It is not basic in action, but is, on the contrary, quite strongly acid. It is insoluble in neutral solvents and is not readily crystallized except from concentrated hydrochloric acid. The crystals are microscopic in size; on being heated above 300°, they are decomposed without melting.

Citrazinic acid had already been synthesized before Lippmann noted its occurrence in the beet. In 1884 Behrmann and Hofmann [2] prepared the acid by the action of sulphuric or hydrochloric acid on the amides of citric acid:

$$\underset{\text{Triamide of citric acid}}{C_6H_5O_4(NH_2)_3} \rightarrow \underset{\text{Citrazinic acid}}{C_6H_5NO_4} + 2NH_3$$

$$\underset{\text{Diamide of citric acid}}{C_6H_5O_4(OH)(NH_2)_2} \rightarrow C_6H_5NO_4 + NH_3 + H_2O$$

$$\underset{\text{Monamide of citric acid}}{C_6H_5O_4(OH)_2(NH_2)} \rightarrow C_6H_5NO_4 + 2H_2O$$

It is also formed when the trimethyl ester of aconitic acid is treated with aqueous or alcoholic ammonia: [3]

$$\underset{\text{Trimethyl ester of aconitic acid}}{C_6H_3O_6(CH_3)_3} + NH_3 + H_2O \rightarrow \underset{\text{Citrazinic acid}}{C_6H_5NO_4} + 3CH_3OH.$$

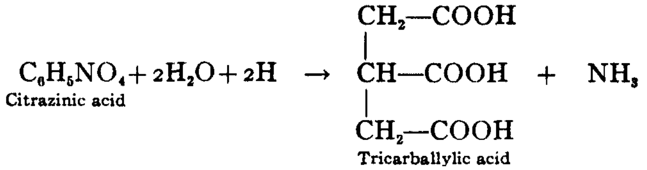
---

[1] von Lippmann, B. **26**, 3061.

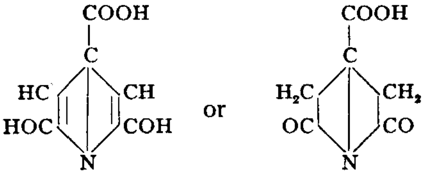
[2] Behrmann and Hofmann, B. **17**, 2681.

[3] Ruhemann, B. **20**, 799, 3366; **21**, 1247; **23**, 831; **27**, 1271. Schneider, B. **21**, 670.

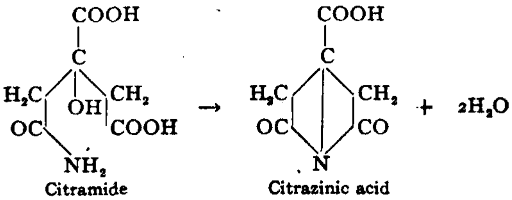
This reaction may be reversed. If citrazinic acid is heated to 180° with hydrochloric acid, it is decomposed into ammonia and aconitic acid.[4] By reduction with tin and hydrochloric acid, it is converted into tricarballylic acid and ammonia:



By treating citrazinic acid with phosphorus pentachloride Behrmann and Hofmann obtained an acid, $C_6H_3Cl_2NO_2$, which when heated with hydriodic acid was converted into isonicotinic acid. From this it follows that citrazinic acid is a *dioxyisonicotinic acid;* its constitution must then be represented by one of the two following formulæ:



The $\alpha\alpha'$-position of the hydroxyl groups (or the carbonyl groups) is naturally derived from the above formation of citrazinic acid from citric and aconitic acids:



This position is further confirmed by investigations of Sell and Dootson.[5]

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[4] Guthzeit and Dressel, A. 262, 89.
[5] Sell and Dootson, Soc. 77, 233.

CHAPTER XVI.

THE TOBACCO ALKALOIDS.

For many years it was supposed that the leaves of the tobacco-plant (*Nicotiana tabaccum* L., family of the Solanaceæ) contained but one alkaloid, nicotine. In 1901, however, Pictet and Rotschy [1] showed that there are present in tobacco, as in most alkaloid-bearing plants, several organic bases.

Thus far the following four alkaloids have been isolated:

Nicotine.....................	$C_{10}H_{14}N_2$
Nicotimine..................	$C_{10}H_{14}N_2$
Nicoteïne...................	$C_{10}H_{12}N_2$
Nicotelline.................	$C_{10}H_8N_2$

These alkaloids are found in the aqueous extract from tobacco; in their separation advantage may be taken of the fact that the first two are volatile with steam. The last three have been separated in very small quantities as compared with nicotine; of the entire alkaloidal content of the aqueous extract, nicoteïne forms possibly 2%, nicotimine ½%, and nicotelline $\frac{1}{10}$%.

In the plant these alkaloids are in combination chiefly with malic and citric acids, to a less extent with oxalic, tartaric, and succinic acids.

1. NICOTINE.

Nicotine was isolated from the leaves of the tobacco-plant by Posselt and Reimann [2] in 1828. The quantity found in the

[1] Pictet and Rotschy, B. 34, 696.

[2] Posselt and Reimann, *Magazin für Pharmacie*, 24, 138.

plant varies considerably (0.6–8%); in general the better grades of tobacco contain the smaller amounts of the alkaloid.

The empirical formula of nicotine, $C_{10}H_{14}N_2$, was established by Melsens [3] in 1843.

Nicotine is a colorless liquid which boils without decomposition at 245°, but does not solidify at −30°; its specific gravity is 1.01 at 20°. In the pure condition it is almost odorless and acquires the odor peculiar to tobacco only after standing for some time in contact with the air. Its taste is sharp and burning. It is very hygroscopic and dissolves readily in water and the ordinary organic solvents. The free alkaloid is strongly lævo-rotatory; its salts, on the contrary, are dextrorotatory.

Nicotine is one of the most active poisons with which we have to deal; the inhalation of its vapor even in small quantities occasions difficulty in breathing.

It is a diacid base and forms salts with one or two equivalents of acid. It unites with two molecules of an alkyl iodide.[4] With methyl iodide it forms two isomeric methiodides: the first is obtained by directly mixing equimolecular quantities of the two substances; the second by treating the monohydriodide of nicotine with an excess of methyl iodide and afterwards eliminating the hydriodic acid by means of sodium carbonate.[5]

These results indicate that nicotine is a bitertiary base. In apparent contradiction to them, however, is an observation of Etard [6] that the alkaloid with acetyl and benzoyl chloride yields an acetyl and a benzoyl derivative.

But, as Pinner [7] has shown, this contradiction is only apparent. If the acetyl- or benzoyl-nicotine of Etard is saponified, nicotine is not again obtained, but an isomeric base, which has received the name *metanicotine.* This is an oily liquid which is optically inactive and boils at 275–278°. It forms a secondary base;

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[3] Melsens, A. ch. [3] **9**, 465.
[4] Kekulé and von Planta, A. **87**, 2. Stahlschmidt, A. **90**, 222.
[5] Pictet and Genequand, *Chemiker-Zeitung*, **21**, 246.
[6] Etard, C. r. **97**, 1218; **117**, 170, 278; Bl. [2] **42**, 297; [3] **14**, 342.
[7] Pinner, B. **27**, 1053, 2861; **28**, 456.

treated with acetic anhydride or benzoyl chloride, it yields the acetyl or benzoyl derivative from which it was obtained. From this Pinner concludes that these are not derivatives of nicotine itself, but of metanicotine, and that in the reaction in which they are formed tertiary nicotine is probably transformed to secondary metanicotine. We shall return to this reaction later on.

Nicotine is an unsaturated body. When heated to 260° with hydriodic acid and red phosphorus it is reduced to *dihydronicotine*, $C_{10}H_{16}N_2$, a lævorotatory liquid boiling at 263–264°. On treatment with sodium and alcohol it adds six or eight atoms of hydrogen and yields hexahydronicotine and octohydronicotine.

Hexahydronicotine, $C_{10}H_{20}N_2$, first obtained by Liebrecht,[8] has been studied chiefly by Blau.[9] It is a solid which melts near 30° and boils at 245°.5. It dissolves readily in water, alcohol, and ether, and closely resembles piperidine in odor. It is a diacid base of secondary-tertiary character (mononitroso-derivative).

Octohydronicotine, $C_{10}H_{22}N_2$, is a liquid which boils at 259–260°. It yields with nitrous acid a dinitroso-derivative and it is consequently a bi-secondary base.

On passing the vapor of nicotine through a tube heated to redness, Cahours and Etard[10] obtained hydrogen, ammonia, hydrocyanic acid, methane, ethane, ethylene, propylene, and pyridine bases.

Among these last they isolated β-propylpyridine, a lutidine, a picoline, and pyridine. The presence of these bases has also been determined in tobacco-smoke.[11]

Oxidation of Nicotine.—Nicotine is readily oxidized; on exposure to the air it absorbs oxygen, turning brown in color. Under the action of oxidizing agents it yields different products whose study has thrown much light on the constitution of the alkaloid.

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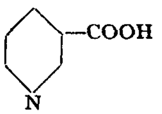
[8] Liebrecht, B. **18**, 2969; **19**, 2587.

[9] Blau, B. **24**, 326; **26**, 628, 1029; **27**, 2535; M. **13**, 330.

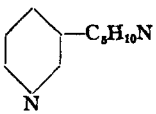
[10] Cahours and Etard, C. r. **88**, 999; **90**, 275; **92**, 1079; Bl. [2] **33**, 951; 34, 449.

[11] Vohl and Eulenberg, A. Pharm. **147**, 130. Kissling, *Dingler's polytechnisches Journal*, **244**, 64, 234. Le Bon and Noel, C. r. **90**, 1538.

By the action of chromic acid on nicotine, Huber[12] in 1867 obtained an acid of the formula $C_6H_5NO_2$, which he named *nicotinic acid.* Later the same result was attained by Weidel[13] and Laiblin[14] by using nitric acid or potassium permanganate. Now nicotinic acid we found to be β-pyridine carboxylic acid (page 57); nicotine is accordingly a pyridine derivative having in the β-position the group $—C_5H_{10}N$:



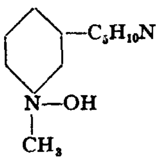
Nicotinic acid



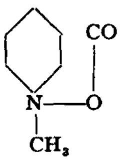
Nicotine

The oxidation of the quaternary derivatives of nicotine leads to a like result. We have seen that nicotine yields two monomethiodides. One of these is formed by treating the monohydriodide of the alkaloid with methyl iodide. In this derivative, then, the methyl iodide is attached to that nitrogen atom which is less strongly basic.

On changing this methiodide to the hydroxide and oxidizing it with potassium permanganate, Pictet and Genequand[15] obtained *trigonelline* (the methyl betaïne of nicotinic acid):



Nicotine monomethyl hydroxide



Trigonelline

This result seems to indicate that the nitrogen atom of the pyridine nucleus is less basic than the other, and that in the

[12] Huber, A. 141, 271; B. 3, 849.
[13] Weidel, A. 165, 328.
[14] Laiblin, A. 196, 129; B. 10, 2136; 13, 1212, 1996.
[15] Pictet and Genequand, B. 30, 2117.

monacid salts of the alkaloid the acid is attached to the nitrogen of the group $C_5H_{10}N$.

With weaker oxidizing agents nicotine yields other oxidation-products. Heating it with mercuric oxide to 240° gives rise to *oxytrinicotine*, $C_{30}H_{27}N_6O_2$. Hydrogen peroxide oxidizes nicotine to a base, *oxynicotine* (*nicotine oxide*), $C_{10}H_{14}N_2O$.[16]

Under the action of potassium ferricyanide in alkaline solution, of silver oxide, or of silver acetate, nicotine loses four atoms of hydrogen and is converted into a base, ***nicotyrine***, $C_{10}H_{10}N_2$. Cahours and Etard, who first obtained this substance, gave it the name *isodipyridine*. When, however, it was shown that nicotine is not a dipyridyl derivative, as it had been supposed to be, Blau proposed that the name be changed to nicotyrine.

Nicotyrine is a colorless, oily liquid which boils at 280–281°. It is little soluble in water; its odor is characteristic. Unlike nicotine, nicotyrine is optically inactive.

Action of Bromine on Nicotine.—This action has been studied by Pinner.[17] When a solution of nicotine in acetic acid is treated at the ordinary temperature with bromine there is formed a perbromide, $C_{10}H_{11}Br_5N_2O$. Boiling water, ammonia, or sulphurous acid serve to convert the latter into ***dibromcotinine***, $C_5H_4N—C_5H_6Br_2NO$ (prisms melting at 125°). On oxidation dibromcotinine yields nicotinic acid—a reaction which indicates that the pyridine nucleus of the molecule has not been affected by the bromine. On reduction with zinc-dust and dilute hydrochloric acid, it is converted into ***cotinine***, $C_{10}H_{12}N_2O$. Cotinine forms a mass of radiating crystals which melt at 50°; it boils at 336°. Both dibromcotinine and cotinine are monacid bases.

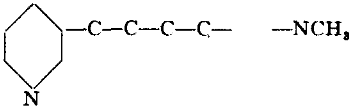
If nicotine is heated to 100° with bromine in a solution of hydrobromic acid, it yields the hydrobromide of ***dibromticonine***, $C_5H_4N—C_5H_4Br_2NO_2.HBr$. The free dibromticonine forms granular crystals which melt at 196°. It is likewise a monacid

[16] Pinner and Wolffenstein, B. **24**, 61, 1378; **25**, 1428. Auerbach and Wolffenstein, B. **34**, 2411.

[17] Pinner, B. **25**, 2807; **26**, 292, 765; **27**, 2861; **28**, 18, 1932.

base, and on oxidation yields nicotinic acid. Reduction with zinc-dust in alkaline solution gives rise to *monobromticonine*, $C_5H_4N—C_5H_5BrNO_2$.

When heated with baryta-water to 100°, dibromticonine is decomposed into nicotinic acid, malonic acid, and methylamine. This decomposition indicates that nicotine contains the atomic groups



Inactive Nicotine.—Nicotine possesses a high specific rotatory power ($[\alpha]_D^{20} = -166°.33$). The conversion of the active alkaloid into the inactive form is effected by heating an aqueous solution of the monochloride or sulphate for some time at about 200°. Pictet [18] thus reduced the specific rotation to − 3°.95, which represents a conversion into inactive nicotine to the extent of 97.7%.

In nearly all its properties, save optical activity, *i*-nicotine appears to be identical with the active form. From this Pictet concludes that the former does not constitute a distinct racemic derivative, but is simply a mixture of *d*- and *l*-nicotine.

The separation of *i*-nicotine into its active constituents has been partly effected recently by Pictet and Rotschy.[19] By repeatedly recrystallizing the salt formed with *d*-tartaric acid, a tartrate is obtained whose melting-point, rotatory power, and other properties correspond with those of the salt resulting from the interaction of the same acid and *l*-nicotine. The *l*-nicotine derived from this salt is in all respects identical with the natural alkaloid.

Constitution of Nicotine.—From the oxidation of nicotine to nicotinic acid it is clear that the alkaloid is a pyridine in which a *β*-hydrogen is replaced by the group $C_5H_{10}N$. It remains then to determine the constitution of this group.

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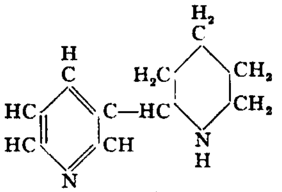
[18] Pictet, **33**, 2355.
[19] Pictet, *work yet unpublished.*

For a long time this complex was regarded as a piperidine ring. What seemed to add particular weight to this opinion was the close resemblance between nicotine and two piperidyl-pyridines which Skraup and Vortmann also Weidel and Russo had prepared by the partial reduction of the dipyridyls (page 76).

Nicotine was accordingly considered to be a piperidyl-pyridine of the following constitution:



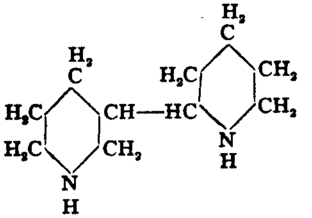
It was soon shown, however, that such a constitution was inadmissible, particularly in the light of the following considerations:

1. Blau* as also Herzig and Meyer[20] found that nicotine possesses a *n*-methyl group, since its hydriodide on decomposition yields the calculated amount of methyl iodide. The formula of the alkaloid may then be written

$$(C_5H_4N)—C_4H_7{=}N—CH_3,$$

which excludes all possibility of the existence of a piperidine nucleus in the molecule.

2. By the reduction of $\alpha\beta$-dipyridyl with sodium and amyl alcohol, Blau obtained *αβ-dipiperidyl* (page 78):



* See note 9, p. 161.

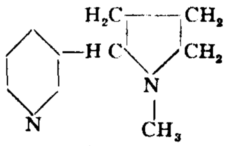
[20] Herzig and Meyer, B. 27, 319; M. 15, 613.

This derivative was, however, not identical with hexahydronicotine.

3. The piperidylpyridine formula for nicotine represents the alkaloid as a secondary-tertiary base. The behavior of nicotine towards alkyl iodides is, however, that of a tertiary base, as has been shown by a number of investigators.

The group $C_5H_{10}N$ is, accordingly, not the piperidine complex. It is furthermore not an open chain, since it contains no double bond.[21]

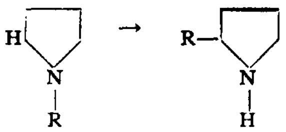
From such considerations Pinner concluded that this group probably contained a pentatomic ring and he accordingly assigned to nicotine the constitution of a *β-pyridyl-α-n-methylpyrrolidine:*



Nicotine

This formula accounts for all the properties and decompositions of nicotine; it explains the constant occurrence of pyrrol derivatives in the dry distillation of salts of the alkaloid; and it has recently been fully established by Pictet [22] in the complete synthesis of *i*-nicotine.

Synthesis of *i*-Nicotine.—From the investigations of Ciamician [23] we know that derivatives of pyrrol containing a *n*-alkyl on being strongly heated undergo a molecular rearrangement, in which the radical shifts from the nitrogen to the α-carbon atom:



[21] Willstätter, B. 28, 2277.

[22] Pictet and Crépieux, B. 28, 1904; 31, 2018. Pictet and Rotschy, B. 33, 2353. Pictet, B. 33, 2355.

[23] Ciamician, B. 18, 1828; 20, 698; 22, 659, 2518.

By subjecting to dry distillation the mucate of β-amidopyridine (page 17) Pictet and Crépieux[24] prepared *n-β-pyridylpyrrol* (a liquid boiling at 251°). This reaction is perfectly analogous to that in which pyrrol itself results from the distillation of ammonium mucate:

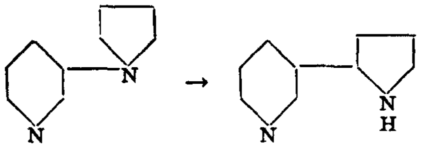
$$\begin{array}{l} CHOH—CHOH—COONH_4 \\ | \\ CHOH—CHOH—COONH_4 \end{array} \rightarrow$$

Ammonium mucate

$$\begin{array}{l} CH{=}CH \\ | \\ CH{=}CH \end{array}\Big> NH + NH_3 + 4H_2O + 2CO_2$$

Pyrrol

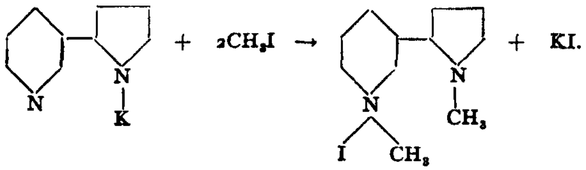
On passing the vapors of *n*-β-pyridylpyrrol through a tube heated to dull redness, these investigators obtained a solid (melting-point 72°), which from the reaction of Ciamician must be regarded as an *αβ-pyridylpyrrol*:



n-β-Pyridylpyrrol αβ-Pyridylpyrrol

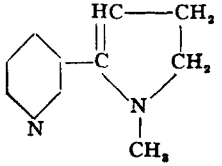
This derivative possesses both basic and acid properties. It reacts with potassium, hydrogen being evolved, and forms a salt in which the hydrogen attached to the nitrogen of the pyrrol nucleus is replaced by the metal. When this salt is warmed with methyl iodide not only does a methyl group take the place of the atom of potassium, but a molecule of the alkyl iodide is also added to the nitrogen of the pyridine nucleus. We thus obtain the *methiodide of n-methyl-αβ-pyridylpyrrol:*

[24] Pictet and Crépieux, B. 28, 1904; 31, 2018.



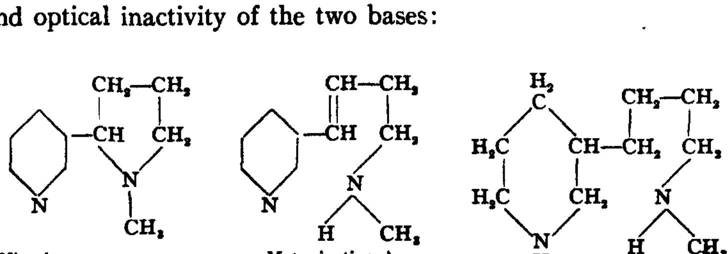
This methiodide is identical with that of nicotyrine and is changed into the free base on distillation over lime. The nicotyrine thus obtained is in all respects identical with the oxidation-product of nicotine.

Its iodo-derivative reduced with tin and hydrochloric acid yields a *dihydronicotyrine*, possibly:



This with bromine forms a perbromide, $C_{10}H_{12}N_2Br_4$, which on reduction with tin and hydrochloric acid is converted into *i-nicotine*.

The formation of metanicotine (page 160) and of octohydronicotine (page 161) is to be accounted for by a rupture of the pyrrolidine nucleus between the nitrogen and the neighboring asymmetric carbon atom. This explains the secondary nature and optical inactivity of the two bases:



Nicotine Metanicotine Octohydronicotine

2. Nicotimine.

This alkaloid is a colorless liquid which boils at 250–255° (uncorrected). It is readily soluble in cold water and all the ordinary organic solvents. Its odor is sharper than that of nicotine and more disagreeable. It is apparently a secondary base, since it yields a nitroso- and a benzoyl-derivative. The alkaloid differs from metanicotine not only in boiling-point, but also in the properties of its salts.

3. Nicoteïne.

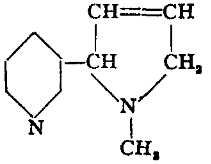
Nicoteïne forms a colorless liquid which boils at 266–267° (uncorrected). Its odor somewhat resembles that of pyrrol, but is quite unlike that of nicotine. The taste of a dilute aqueous solution is sharp and intensely bitter.

Nicoteïne like nicotine is lævorotatory, but its specific rotation is only about one-fourth that of the latter alkaloid.

The salts of nicoteïne like the free base are lævorotatory.

Nicoteïne is a diacid, bitertiary base. In physiological action it resembles nicotine, but its toxicity is apparently greater. Oxidation of the alkaloid with concentrated nitric acid gives rise to nicotinic acid.

The alkaloid closely resembles its isomer, dihydronicotyrine, and it is probable that it possesses a similar constitution. Possibly its constitution may be formulated as follows:



Nicoteïne

4. Nicotelline.

Of the four alkaloids from the tobacco-plant, this alone is a solid at the ordinary temperature.

Crystallized from alcohol or water, nicotelline forms white, prismatic needles which melt at 147–148°. It is little soluble in cold water, but dissolves with considerable readiness in hot. Unlike the other alkaloids of this group, its aqueous solution is neutral toward litmus.

Many of the reactions of nicotelline seem to indicate that its constitution differs fundamentally from that of nicotine and of nicotelline. Too little, however, is as yet known regarding the alkaloid to lead to any definite conclusion.

CHAPTER XVII.

THE JABORANDI ALKALOIDS.

THE leaves of the Jaborandi (*Pilocarpus pennatifolius* Lemaire, family of the Rutaceæ) contain three, possibly four alkaloids:

Pilocarpine..................	$C_{11}H_{16}N_2O_2$
Isopilocarpine..............	"
Pilocarpidine...............	$C_{10}H_{14}N_2O_2$
Jaborine....................	$C_{11}H_{16}N_2O_2$

In the leaves of related species occur still other alkaloids, which closely resemble those just named.[1] Thus in *Aracati jaborandi* and *Pilocarpus spinatus* are found the so-called *pseudo-pilocarpine* and *pseudojaborine*,[2] and in the false Jaborandi *jaborandine*.[3]

1. PILOCARPINE.

This alkaloid was discovered by Hardy in 1875. Since then it has been the subject of numerous investigations,[4] but unfortunately some of these are not as satisfactory as one might wish.

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[1] Paul and Cownley, *Pharm. Jour. and Trans.* **57**, 1.

[2] Petit and Polonovski, J. de Pharm. Chim. [6] **5**, 369, 430; **6**, 8; Bl. **17**, 553, 702.

[3] Parodi, *Revista Pharmaceuta* 1875, 3.

[4] Hardy and Calmels, Bl. [2] **46**, 479; **48**, 220; C. r. **102**, 1116, 1251, 1562; **103**, 277; **105**, 68. Chastaing, C. r. **94**, 223, 968; **97**, 1435; **100**, 1593; **101**, 507. Harnack and Meyer, A. **204**, 67. Knudsen, B. **25**, 2985; **28**, 1762. Jowett, Soc. **77**, 473, 851; **79**, 580, 1331; **83**, 438, 464; Proc. Soc. **16**, 50, 123; **17**, 56, 198; **19**, 54; B. **33**, 2892. Pinner and Kohlhammer, B. **33**, 1424, 2357; **34**, 727. Pinner and Schwarz, B. **35**, 192, 2441.

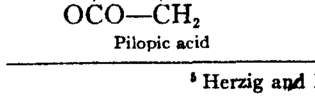
As ordinarily obtained pilocarpine is an oily sirup which when quite pure crystallizes; it is, however, very hygroscopic. It dissolves readily in both water and alcohol, somewhat less readily in ether. Both the free base and its salts are dextrorotatory.[5]

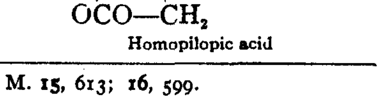
In its physiological action pilocarpine excites the secretion of the perspiration and of the saliva; it acts upon the eye causing, unlike atropine, a contraction of the pupil (myosis). It is interesting to note that pilocarpidine, which is frequently found as an impurity in the pilocarpine commonly obtained, produces like atropine a dilation of the pupil. Administered in larger quantities, pilocarpine is a strong poison whose action resembles that of nicotine.

The alkaloid is a monacid base and has a methyl group attached to one of its two nitrogen atoms. It is soluble in caustic alkalies, and this solubility is made use of in separating pilocarpine from other related alkaloids which do not possess this property.

Pilocarpine is readily converted into its isomer, *isopilocarpine.* To effect this change it is sufficient to heat the hydrochloride of the alkaloid for half an hour at a temperature a few degrees above its melting-point (204–205°), or to distil the free base *in vacuo.* A mixture of the two alkaloids is thus obtained, from which isopilocarpine may be separated.

From the oxidation of pilocarpine with potassium permanganate there result ammonia, methylamine, small quantities of acetic and propionic acids, *pilopic acid*, $C_7H_{10}O_4$, and *homopilopic acid*, $C_8H_{12}O_4$. The last two are lactone acids. When fused with caustic potash the first yields normal butyric acid, the second under the same treatment at a lower temperature forms α-ethyltricarballylic acid, $C_8H_{12}O_6$. Jowett, accordingly, represents these acids by the following formulæ:


Pilopic acid


Homopilopic acid

[5] Herzig and Meyer, M. 15, 613; 16, 599.

On oxidation with chromic acid at the temperature of the water-bath pilocarpine is converted into a dibasic acid, *pilocarpoic acid*, $C_{11}H_{16}N_2O_6$. On further oxidation of this acid with potassium permanganate there is formed a finely crystalline acid, $C_7H_{10}O_5$, of unknown constitution.

On treatment with bromine pilocarpine yields a perbromide, $C_{11}H_{14}N_2O_2Br_2.HBr.Br_2$. By the action of ammonia this perbromide is converted into *dibrompilocarpine*, $C_{11}H_{14}N_2O_2Br_2$ (colorless prisms, melting-point 95°). Reduction of the dibromide gives rise again to pilocarpine. By the action of bromine on pilocarpine at higher temperatures, *bromcarpinic acid*, $C_{10}H_{15}N_2O_4Br$ (prisms, melting-point 209°), is obtained.

2. Isopilocarpine.

The occurrence of this alkaloid in Jaborandi-leaves was noted by Jowett [6] in 1900. Its formation from pilocarpine has already been mentioned (page 172).

Isopilocarpine is an oily liquid which boils at 261° at a pressure of 10 mm. It closely resembles its isomer, pilocarpine. The specific rotatory power of the two alkaloids and the different properties of their salts show clearly, however, that the two substances are different:

Pilocarpine. $[\alpha]_D = +100°.5$	Isopilocarpine. $[\alpha]_D = +42°.8$
Pilocarpine nitrate, M. P. 178°	Isopilocarpine nitrate, M. P. 159°
" hydrochloride, M. P. 204–5°	" hydrochloride, M.P. 127°
" hydrobromide, M. P. 185°	" hydrobromide, M.P. 147°
" methiodide, an oil	" methiodide, M. P. 114°.

Like pilocarpine, isopilocarpine is a monacid base, is soluble in alkalies, and possesses a *n*-methyl. Oxidized with potassium

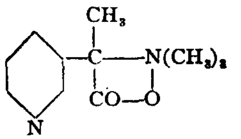
[6] Jowett, Soc. 77, 473.

permanganate it yields the same products as does its isomer. Oxidation with chromic acid, however, does not lead to pilocarpoic acid, but apparently occasions a general disruption of the molecule.

On treatment with bromine, isopilocarpine yields a perbromide, $C_{11}H_{14}N_2O_2Br_2HB.Br_2$, which can be readily converted into *dibromisopilocarpine*, $C_{11}H_{14}N_2O_2Br_2$ (prisms, melting-point 135°). If the dibromide is reduced, isopilocarpine is again formed. If the dibromide is oxidized with potassium permanganate, there are formed ammonia, methylamine, pilopic acid, $C_7H_{10}O_4$, and a new acid, *pilopinic acid*, $C_8H_{11}NO_4$ (melting-point 98°).

When bromine acts upon isopilocarpine at a higher temperature the two chief products formed are *dibromisopilocarpinic acid*, $C_{11}H_{14}N_2O_4Br_2$, and *monobromisopilocarpinic acid*, $C_{11}H_{15}N_2O_4Br$. The first acid crystallizes in well-defined rectangular prisms which melt with decomposition at 235°.

Constitution of Pilocarpine and Isopilocarpine.—From their investigations Hardy and Calmels decided that the constitution of pilocarpine was to be represented by the formula



The account of their work, however, is unsatisfactory and incomplete and, as later investigations have shown, unreliable.

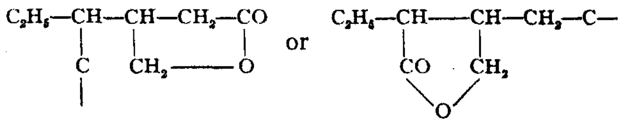
Our knowledge regarding the constitution of these alkaloids we owe chiefly to the recent work of the two investigators Jowett and Pinner.

Since both pilocarpine and isopilocarpine on oxidation with potassium permanganate yield the potassium salt of a hydroxy-acid, $C_8H_{14}O_5$, of which homopilopic acid, $C_8H_{12}O_4$ (page 172), is the lactone acid, and since the hydroxy-acid has been deter-

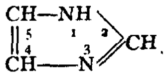
mined with a high degree of probability to be

$$C_2H_5—CH(CO_2H)—CH(CH_2OH)—CH_2(CO_2H),$$

we may assume that the alkaloids contain one of the following complexes:



From certain analogies found to exist between pilocarpine derivatives and glyoxaline Pinner and Schwarz concluded that the alkaloids probably contained the glyoxaline ring:



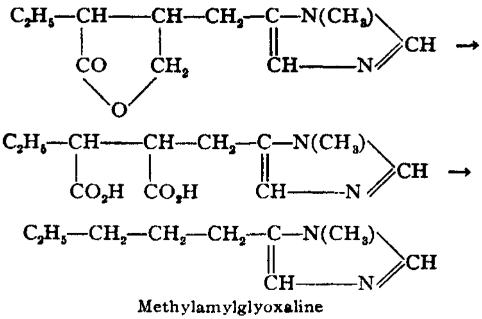
Glyoxaline

Jowett then called attention to the close resemblance in behavior between isopilocarpine and dimethylglyoxaline.

The probable presence of a glyoxaline nucleus in the molecule received conclusive proof, as shown by the latter investigator, from the formation of various glyoxaline derivatives by the distillation of isopilocarpine with soda-lime. The crude product obtained from this distillation was found to contain 1-*methylglyoxaline*, 1,4- (or 1,5-) *dimethylglyoxaline*, 1,4- (or 1,5-) *methylamylglyoxaline*, and probably 1,4- (or 1,5-) *methylamyleneglyoxaline*, together with ammonia and methylamine.

The formation of these derivatives is readily explained by supposing that the CH_2OH group is oxidized to carboxyl with subsequent elimination of carbon dioxide, yielding methylamylglyoxaline.

Assuming the following formula for isopilocarpine, the change might be thus represented:

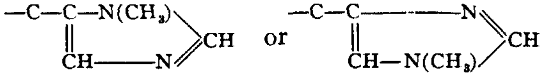


Methylamylglyoxaline

The other glyoxalines, as well as ammonia and methylamine, are produced by further disruption of the molecule and final fission of the glyoxaline ring itself.

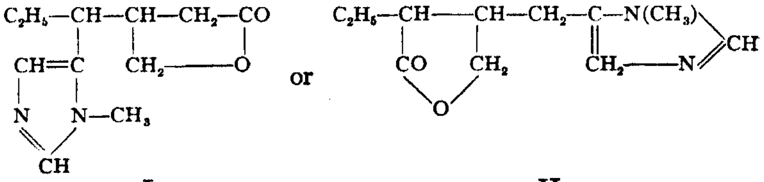
It seems evident, then, that isopilocarpine must be regarded as a glyoxaline derivative. It remains to determine (*a*) the point of attachment of the glyoxaline and homopilopic complexes, and (*b*) the appropriate formula for the homopilopic residue.

Since 1,4- (or 1,5-) dimethylglyoxaline is formed in the distillation with soda-lime, one of the following complexes must exist in isopilocarpine:



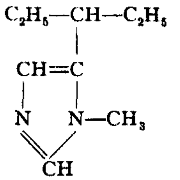
Inasmuch as it is at present impossible to decide between these formulæ, we may arbitrarily assume that isopilocarpine is a 1,5-glyoxaline derivative.

From the two possible homopilopic complexes, isopilocarpine will then be



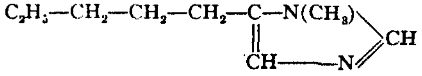
I II

The determination of the constitution of the methylamylglyoxaline formed above renders it possible to decide between these two formulæ. From the reactions probably involved in its formation (page 175) this glyoxaline derivative, according as it is derived from formula I or II, will have the following constitution:



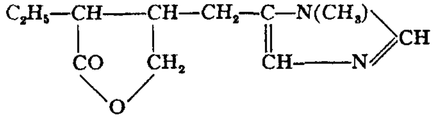
III

or



IV

These compounds on oxidation would yield either (III) diethylacetic acid or (IV) normal hexoic acid. On oxidation normal hexoic acid was obtained, consequently IV represents the methylamylglyoxaline formed. The constitution of isopilocarpine may then be regarded as established with a fair degree of certainty as



Isopilocarpine

Jowett considers that pilocarpine is a stereoisomer of isopilocarpine and is consequently to be represented by the same structural formula.

3. PILOCARPIDINE.

This alkaloid was discovered by Harnack[6] in 1887. The base forms a deliquescent, crystalline mass of strongly alkaline reaction. It is somewhat soluble in water, easily soluble in alcohol and chloroform, and but little soluble in ether and benzol. Both the base and its salts are optically active.

[6] Harnack, A. 238, 228.

Pilocarpidine is a monacid base; it possesses at the same time acid properties, however, and unites with alkalies to form salts which have the general formula $C_{10}H_{18}N_2O_2M$, and which are readily decomposed by carbonic acid.

Heated with potassium hydroxide to 200°, the alkaloid gives off dimethylamine.[7]

According to Herzig and Meyer[8] pilocarpidine contains no *n*-methyl. When an acid solution of the base is evaporated it is stated that a new alkaloid, *jaboridine*, $C_{10}H_{12}N_2O_3$, is formed.

4. JABORINE.

In 1880 Harnack and Meyer[9] isolated from the leaves of the Jaborandi a base which they supposed to be an isomer of pilocarpine and to which they gave the name of jaborine. They describe the alkaloid as an amorphous substance soluble in alcohol and ether.

From the work of Jowett[10] it seems not improbable that jaborine is a mixture of pilocarpidine, isopilocarpine, and possibly a trace of pilocarpine.

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[7] Merck, *Bericht für* 1896.
[8] Herzig and Meyer, M. **18**, 379; **19**, 56.
[9] Harnack and Meyer, A. **204**, 67.
[10] Jowett, Soc. **77**, 492.

CHAPTER XVIII.

CYTISINE.

CYTISINE was discovered in 1865 by Husemann and Marmé[1] in the seeds of *Cytisus laburnum* L. It has been found furthermore in various species of *Cytisus*, *Ulex*, *Genista*, *Sophora*, *Baptisia*, and *Euchresta*. All these plants belong to the pulse family (*Leguminosæ*).

The formula of cytisine is $C_{11}H_{14}N_2O$. It crystallizes from alcohol in prisms which melt at 152–153° and which can be sublimed *in vacuo* without decomposition. The alkaloid is quite soluble in water, alcohol, and chloroform, difficultly soluble in ether and benzol, and insoluble in ligroin.

Cytisine is a diacid base; it is strongly alkaline in its reaction; it expels ammonia from ammonium salts and precipitates the oxides of the heavy metals from their salt solutions. Its taste is both bitter and caustic and it acts as a violent poison. It turns the plane of polarized light to the left.

The alkaloid has been studied with reference to its chemical properties and constitution by a number[2] of investigators. Through their work the following points have been established:

Cytisine is both a secondary and a tertiary base; it yields a nitrosamine (needles, melting-point 174°) and a monacetyl derivative (melting-point 208°). No methyl group is attached to either nitrogen atom.[3] With methyl iodide it forms a biter-

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[1] Husemann and Marme, *Zeitschrift für Chemie*, 1865, 161; 1869, 677.

[2] Plugge, A. Pharm. **229**, 48, 561; **232**, 444; **233**, 294, 430, 441. Partheil, B. **23**, 3201; **24**, 634; A. Pharm. **231**, 448; **232**, 161, 486; *Apotheker-Zeitung*, **10**, 903. Buchka and Magahaes, B. **24**, 253, 674. Rauwerda, A. Pharm. **238**, 477. Freund and Friedmann, B. **34**, 615.

[3] Herzig and Meyer, M. **18**, 379.

tiary methylcytisine, $(C_{11}H_{13}NO)=NCH_3$ (melting-point 134°), which may further be converted into the monomethiodide, $(C_{11}H_{13}NO)=N(CH_3)_2I$. When this last is heated with caustic potash, there is obtained a new tertiary base, *dimethylcytisine*:

$$\underset{\text{Methiodide of methylcytisine}}{(C_{11}H_{13}NO)N(CH_3)_2I} + KOH \rightarrow \underset{\text{Dimethylcytisine}}{(C_{11}H_{12}NO)N(CH_3)_2} + KI + H_2O.$$

Dimethylcytisine in turn will add methyl iodide and the addition-product on treatment with caustic potash is decomposed into trimethylamine, formaldehyde, and an amorphous base of the composition $C_{10}H_{13}NO_2$, whose constitution, however, has not yet been determined:

$$(C_{11}H_{12}NO)N(CH_3)_3I + KOH + H_2O \rightarrow C_{10}H_{13}NO_2 + (CH_3)_3N + CH_2O + KI.$$

In the action of methyl iodide on cytisine, it follows that only the secondary nitrogen atom is affected.

Hydrogen peroxide oxidizes cytisine to an *oxycytisine*, $C_{11}H_{14}N_2O_2$, which possesses the properties of a hydroxylamine derivative. Oxycytisine, $C_{11}H_{13}O(N—OH)$, melts with decomposition at 223–226°; it reduces an ammoniacal silver solution, but is otherwise quite stable in the presence of alkalies or acids. It is basic and at the same time weakly acid.

Bromine acts upon the alkaloid, giving a dibromcytisine, $C_{11}H_{12}Br_2N_2O$ (melting-point 63°). Cytisine contains no methoxy group; distilled over zinc-dust or soda-lime it forms pyrrol and pyridine bases. On oxidation with potassium permanganate it is converted into oxalic acid and ammonia.

According to van de Moer [4] cytisine is formed from pilocarpine hydrochloride when the latter in a solution of chlorine-water is exposed to the action of direct sunlight. Pilocarpine, $C_{11}H_{16}N_2O_2$, indeed, differs from cytisine, $C_{11}H_{14}N_2O$, in composition only by an additional molecule of water, yet this rather strange obser-

[4] van de Moer, *Berichte der deutschen pharmaceutischen Gesellschaft*, 5, 257.

vation of van de Moer's needs to be confirmed. An apparently insuperable objection to any such reaction is the fact that cytisine, unlike pilocarpine, possesses no methyl group attached to nitrogen.

Cytisine has proved to be identical with several alkaloids to which formerly different names were applied, as *ulexine*[5] (*Ulex europaeus*), *baptitoxine* (*Baptisia tinctoria*), and *sophorine* (*Sophora tomentosa*).

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[5] Gerraro, *Pharm. Journal and Trans.* 1886 [3], XIII, 101.

CHAPTER XIX.

SPARTEÏNE.

SPARTEÏNE, $C_{15}H_{26}N_2$, was discovered by Stenhouse[1] in 1851 in *Spartium scoparium* L. (family of the Leguminosæ). The alkaloid is an oily liquid which distils without decomposition at 288° (311° according to Bamberger[2]); it possesses a faint odor, somewhat resembling that of aniline, and a very bitter taste; it is poisonous, its action being that of a narcotic.

Sparteïne is readily soluble in alcohol, ether, and chloroform; it is, however, insoluble in benzol and ligroin and very little soluble in water. Its density is somewhat greater than that of water. It is optically active, turning the plane of polarization to the left.

As yet we know little in regard to the constitution of this alkaloid. Certain facts have, however, been established. It is a diacid, bitertiary base[3] and contains a pyridine ring. By distilling sparteïne over lime or by passing its vapor through a tube heated to redness, Ahrens[4] obtained pyridine, γ-picoline, ammonia, prussic acid, ethylene, propylene, and other hydrocarbons. By heating sparteïne sulphate with zinc-dust, the same investigator got pyridine, α-picoline, a trimethylpyridine (possibly $\alpha\beta\alpha'$), methyldiethylamine, etc.

On oxidation with potassium permanganate, the base yields, according to Bernheimer,[5] a pyridine carboxylic acid, together with a large quantity of oxalic and formic acids. When sparteïne

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[1] Stenhouse, *Philosophical Transactions*, 1851 [2], 422; A. **78**, 15.

[2] Bamberger, A. **235**, 368.

[3] Mills, A. **125**, 71.

[4] Ahrens, B. **20**, 2218; **21**, 825; **24**, 1095; **25**, 3607; **26**, 3035; **30**, 195.

[5] Bernheimer, G. **13**, 451.

is heated with silver oxide to 170–180°, it is decomposed, forming pyridine and carbon dioxide.[6]

Ahrens claims that by heating sparteïne with hydriodic acid to 200°, methyl iodide is split off and a secondary base, $C_{14}H_{24}N_2$, is formed. Herzig and Meyer,[7] as also Moureu and Valeur,[8] have, however, been unable to detect the presence of any methyl group attached to nitrogen.

Sparteïne is an unsaturated body; with tin and hydrochloric acid it is reduced to *dihydrosparteïne*, $C_{15}H_{28}N_2$. This is a heavy liquid, which boils at 281–284°. It is a secondary base, little soluble in water.

Sparteïne is very easily affected by oxidizing agents. By the action of a number of these, such as "chloride of lime," hydrogen peroxide, lead peroxide, silver oxide, etc., Ahrens obtained a series of oxidation-products. These have, however, contributed nothing further to our knowledge of the constitution of the alkaloid. The chief of these oxidation-products are:

a. *Dehydrosparteïne*, $C_{15}H_{24}N_2$, a liquid which boils at 314–315°.

b. *Oxysparteïne*, $C_{15}H_{24}N_2O$ ($C_{14}H_{23}N_2(COH)$?), needles melting at 83–84°, a diacid base possessing the properties of an aldehyde. Phosphorus oxychloride causes the elimination of a molecule of water with the formation of a volatile base, $C_{15}H_{22}N_2$.

c. Two isomeric bases of the composition $C_{15}H_{26}N_2O$. These are oily liquids.

d. *Dioxysparteïne*, $C_{15}H_{24}N_2O_2$ ($C_{15}H_{22}N_2(OH)_2$?), prisms melting at 128–129°. Heated with concentrated hydrochloric acid it is converted into dehydrosparteïne.

e. *Trioxysparteïne*, $C_{15}H_{24}N_2O_3$, a monacid base, crystalline, but quite deliquescent.

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[6] Peratoner, G. **22**, 555.

[7] Herzig and Meyer, M. **15**, 613; **16**, 599.

[8] Moureu and Valeur, C. r. **137**, 194.

CHAPTER XX.

THE LUPINE ALKALOIDS.

THE seeds of the yellow lupine (*Lupinus luteus* L., family of the Leguminosæ) contain before or after their germination a large number of substances: albuminous matter (as high as 49%), a glucoside of the formula $C_{29}H_{32}O_{16}$, acids (malic, citric, oxalic), and an entire series of basic derivatives, which are mostly decomposition-products of albuminous bodies: asparagine (17-19%), leucine, phenylalanine, tyrosine, arginine, choline, xanthine, hypoxanthine, *lupinine*, *lupinidine*, etc. We will consider here only the two last alkaloids, which are quite distinct from the others and are alone characteristic of the yellow lupine.

These alkaloids are found only in the yellow and black lupine (*Lupinus niger*);[1] the seeds of the white lupine (*Lupinus albus* L.) contain two other alkaloids, *dextro-lupanine* and *inactive lupanine*. Dextro-lupanine is also obtained from the seeds of the blue lupine (*Lupinus angustifolius* L.) and from those of the wild lupine (*Lupinus perennis* L.).[2]

1. LUPININE.

Lupinine was discovered by Cassola[3] in 1835. It has been studied in a more or less impure condition by a number of investigators. In 1881 it received from Baumert[4] the formula $C_{21}H_{40}N_2O_2$, which was generally accepted. The recent work

[1] Schmidt and Behrend, A. Pharm. **235**, 262.
[2] Schmidt and Davis, A. Pharm. **235**, 192, 218, 229.
[3] Cassola, A. **13**, 308.
[4] Baumert, B. **14**, 1150, 1321, 1880, 1882; **15**, 631, 1951; A. **214**, 361; **224**, 313.

of Willstätter and Fourneau,[5] however, indicates that the composition of the alkaloid must be represented by the simpler formula $C_{10}H_{19}NO$.

Lupinine is a crystalline substance which melts at 68–69° and distils without decomposition at 255–257° in an atmosphere of hydrogen. It possesses an agreeable fruit-like odor, a very bitter taste, and is only weakly poisonous. It is readily soluble in water, alcohol, and ether, and is volatile with steam.

The alkaloid is a tertiary base, in optical activity strongly lævorotatory; it contains a hydroxyl group. When subjected to exhaustive methylation it yields trimethylamine and a non-nitrogenous, unsaturated body possessing the properties of an alcohol. The successive reactions may be represented as follows:

$$(C_{10}H_{19}O)\equiv N\begin{cases}CH_3\\OH\end{cases} \rightarrow H_2O + (C_{10}H_{18}O)=N-CH_3$$

$$(C_{10}H_{18}O)=N\begin{cases}CH_3\\CH_3\\OH\end{cases} \rightarrow H_2O + (C_{10}H_{17}O)-N\begin{cases}CH_3\\CH_3\end{cases}$$

$$(C_{10}H_{17}O)-N(OH)\begin{cases}CH_3\\CH_3\\CH_3\end{cases} \rightarrow H_2O + N(CH_3)_3 + C_{10}H_{15}(OH)?$$

On oxidation with chromic acid lupinine yields a monocarboxylic acid, *lupinic acid*, $(C_9H_{16}N)CO_2H$, which crystallizes in prisms (from acetone) and melts at 255°. With dehydrating agents the alkaloid loses a molecule of water and is converted into *anhydrolupinine*, $C_{10}H_{17}N$.

2. LUPINIDINE.

Lupinidine, $C_8H_{15}N$, was also studied by Baumert.[6] It is an oily, easily oxidizable base of tertiary character, heavier than

[5] Willstätter and Fourneau, B. **35**, 1910; A. Pharm. **240**, 335.
[6] Baumert, A. **224**, 321; **225**, 365; **227**, 207.

water and volatile with steam. In cold water it is more readily soluble than in hot; in alcohol and ether it is quite soluble. In odor it resembles conine, in taste it is bitter. It is weakly poisonous. The salts of lupinidine like those of lupinine are lævorotatory.

3. DEXTRO-LUPANINE.

This alkaloid, $C_{15}H_{24}N_2O$, was discovered in 1885 by Hagen [7] in the seeds of the blue lupine; it is also found in those of the white and of the wild lupine.

It has been studied by Soldaini,[8] Schmidt and Siebert,[9] and Schmidt and Davis. The first of these investigators described the alkaloid as a yellow, sirupy substance. Schmidt and Davis, however, succeeded in obtaining dextro-lupanine, by crystallization from ligroin, in the form of small needles which melt at 44°. It is easily soluble in cold water, but separates from the solution when the latter is heated; it is also readily soluble in alcohol, ether, chloroform, and ligroin. It cannot be distilled. The free base and its salts are dextrorotatory. In taste it is bitter, and in physiological action poisonous.

Lupanine is a strong, monacid, tertiary base; it contains apparently no methoxyl, carbonyl, hydroxyl, ketone, or aldehyde group; no methyl group is attached to the nitrogen. Treated with sodium and alcohol, it is said to add four and six atoms of hydrogen; this is, however, disputed by Callsen.[10]

By the prolonged action of an alkali it is decomposed with the formation of ammonia, a hydrocarbon, and a base, C_7H_9N, which is probably a dimethylpyridine. Also on distillation over soda-lime there are formed ammonia and a pyridine base.

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[7] Hagen, A. **230**, 367.

[8] Soldaini, A. Pharm. **230**, 61; **231**, 321, 481; G. **23**, [1] 143; **25**, [1] 352; **27**, [2] 191; **32**, [1] 389; **33**, [1] 428; *Boll. Chim. Farm.* **41**, 37; **42**, 113.

[9] Schmidt and Siebert, A. Pharm. **229**, 531.

[10] Callsen, *Inaugural-Dissertation* 1898, Marburg.

When lupanine is warmed with bromine in an alcoholic solution it is decomposed according to the following equation:

$$C_{15}H_{24}N_2O + H_2O \rightarrow C_8H_{15}NO + C_7H_{11}NO.$$

Of the two bases thus obtained, the former has been the better studied; it is isomeric with tropine, possesses the nature of a tertiary base and by the action of hydrochloric acid loses a molecule of water, there being formed the base $C_8H_{13}N$. Both the bases resulting from the decomposition of lupanine contain a hydroxyl group. This is shown by the formation of their acetyl derivatives. Since dextro-lupanine itself contains no hydroxyl, its general formula may be thus expressed:

$$\begin{array}{l} C_8H_{14}N \\ | \\ O \\ | \\ C_7H_{10}N. \end{array}$$

4. Inactive lupanine

This alkaloid was discovered by Soldaini in 1892 and has been studied by Schmidt and Davis. It crystallizes from ligroin in needles which melt at 99°; it is easily soluble in water, alcohol, ether, chloroform, and ligroin. It is a monacid, tertiary base, in reaction strongly alkaline. On being heated, it emits the odor of pyridine.

Inactive lupanine is a racemic mixture, being composed of equal parts of dextro- and lævo-lupanine.

On preparing its sulphocyanate, Schmidt and Davis obtained two sorts of hemimorphic crystals which melt at 188°. These were separated and decomposed by an alkali. The two bases thus prepared differed only in the sign of their optical activity. The dextro-modification proved to be identical with the dextro-lupanine already studied.

CHAPTER XXI.

THE SOLANUM ALKALOIDS.

SEVERAL plants from the family of the Solanaceæ are characterized by the presence in their tissues of some very poisonous alkaloids which in their chemical properties and constitution closely resemble one another. These plants are:

the belladonna (*Atropa Belladonna* L.),
the henbane (*Hyoscyamus niger* L. and *H. albus* L.),
the common stramonium (*Datura Stramonium* L.),
the *Duboisia myoporoides* R. Br.,
and different species of the genus *Scopolia*.

The solanum alkaloids are found in all parts of the plant, but particularly in the seeds and roots; the quantity of alkaloid found, however, is inconsiderable, never amounting to more than 0.6% of the plant.

The bases of the Solanaceæ were for a long time separated with difficulty, since they behave quite similarly and are furthermore easily converted into one another. We can, however, consider as safely established to-day the existence of the following seven alkaloids:

1. Atropine, $C_{17}H_{23}NO_3$.
2. Hyoscyamine, "
3. Pseudohyoscyamine, "
4. Hyoscine, "
5. Atropamine, $C_{17}H_{21}NO_2$.
6. Belladonnine, "
7. Scopolamine (atroscine), $C_{17}H_{21}NO_4$.

Of these seven alkaloids, atropine, hyoscyamine, and scopolamine are found in all the plants above named; atropine occurs especially in the berries of the belladonna, or deadly night-shade, while hyoscyamine and scopolamine appear chiefly in the seeds of the henbane. Atropamine and belladonnine have as yet been found only in the deadly night-shade; pseudohyoscyamine has been observed in *Duboisia myoporoides*, hyoscine in the henbane.

1. ATROPINE.

Atropine was discovered in 1831 almost simultaneously by Mein [1] and by Geiger and Hesse [2] in the roots of the belladonna. The base crystallizes from alcohol and chloroform in prisms which melt at 115–116°; in both these liquids it is easily soluble, less so in ether and benzol and soluble with difficulty in cold water. Its solutions have a sharp, bitter taste and are without action on polarized light. It is a strong poison; its widespread use in medicine is due to its action, causing dilation of the pupil (mydriasis).

As Will [3] and Schmidt [4] have shown, atropine is formed from its stereoisomer, hyoscyamine, by heating the latter in the absence of air to 110°, or from its alcoholic solution when this stands for a time after the addition of a few drops of an alkali or even stands for a longer time by itself.[5] This change is only a stereochemical one. The structure of the two alkaloids, as we shall see farther on, is the same and, according to Ladenburg,[6] Gadamer,[7] and Amenomiya,[8] they differ only in that hyoscyamine is the lævo-modification and atropine the racemic form. The separation of the latter into its constituents has, however, not as yet

[1] Mein, A. 6, 67.
[2] Geiger and Hesse, A. 7, 269.
[3] Will, B. 21, 1717, 2777.
[4] Schmidt, B. 21, 1829.
[5] Hesse, A. 309, 75.
[6] Ladenburg, B. 21, 3065.
[7] Gadamer, A. Pharm. 239, 294.
[8] Amenomiya, A. Pharm. 240, 498.

been effected, although the constituents themselves have apparently been synthesized.

The ease of transformation of hyoscyamine into atropine caused Will[8] to suspect that the latter really does not exist in the plant, but that it is formed by the treatment which is employed in the extraction and purification of the alkaloids and in the course of which the base is repeatedly brought in contact with alkali and is also more or less heated. In these operations it is reasonable to suppose, indeed, that hyoscyamine is partly converted into atropine, but the investigations of several chemists, particularly those of Schmitt and Schütte,[9] warrant us in assuming the existence of atropine with hyoscyamine in the plant.

Atropine itself in turn may under the influence of various reagents lose a molecule of water and be converted into other alkaloids. Thus Pesci[10] in 1882 observed that with fuming nitric acid it gives rise to a base which he named *apoatropine* and which was later found to be identical with the natural *atropamine*. The same transformation is produced, according to Hesse,[11] by the action of cold sulphuric acid or of acetic or phosphoric anhydride.

If atropine is heated to 130°, it suffers a loss of water in a different direction, a part of the base being converted into belladonnine:

$$\underset{\text{Atropine}}{C_{17}H_{23}NO_3} \rightarrow \underset{\text{Atropamine, or Belladonnine}}{C_{17}H_{22}NO_2} + H_2O.$$

Atropine is a tertiary base. It possesses a hydroxyl group[12] and a methyl group attached to the nitrogen.[13] It is at the same time an ester; for, as Kraut[14] and Lossen[15] showed in 1863, it is saponified by alkalies, baryta-water, or hydrochloric

[9] Schmitt and Schütte, A. Pharm. **229**, 492.
[10] Pesci, G. **12**, 285, 329.
[11] Hesse, A. **277**, 290.
[12] Schmidt, A. Pharm. **232**, 409.
[13] Herzig and Meyer, B. **27**, 319; M. **15**, 613.
[14] Kraut, A. **128**, 273; **133**, 87; **148**, 236.
[15] Lossen, A. **131**, 43; **138**, 230.

acid, forming an acid, *inactive tropic acid*, and an alcamine, *tropine:*

$$\underset{\text{Atropine}}{C_{17}H_{23}NO_3} + H_2O \rightarrow \underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Tropine}}{C_8H_{15}NO}.$$

This saponification of atropine has become of fundamental importance in determining the constitution of the solanum bases.

By further action of the above saponifying reagents, tropic acid itself suffers a loss of one molecule of water, and there is formed a mixture of *atropic acid*, $C_9H_8O_2$, and *isatropic acid*, $C_{18}H_{16}O_4$. On the other hand, by the action of hydrochloric acid at 180°, tropine loses a molecule of water and is converted into *tropidine*, $C_8H_{13}N$.

The partial synthesis of atropine was effected by Ladenburg[16] in 1879 by heating tropine and tropic acid with dilute hydrochloric acid on the water-bath. The reaction is the reverse of that formulated above; the tropine and tropic acid unite with loss of one molecule of water to form atropine.

By the union of other acids with tropine, Ladenburg has prepared an entire series of similar esters which he has named *tropeïnes* and of which some, like atropine, are endowed with mydriatic properties.

2. Hyoscyamine.

Hyoscyamine was obtained in 1833 by Geiger and Hesse[17] from henbane; recently it has also been found in *Hyoscyamus muticus* by Dunstan and Brown[18] and in *Mandragora*-roots by Thoms and Wentzel.[19] Its properties are quite similar to those of atropine.

It crystallizes from alcohol in needles which melt at 108°.5 and which are very readily soluble in alcohol, somewhat less soluble

[16] Ladenburg, B. 12, 941.
[17] Geiger and Hesse, A. 7, 270.
[18] Dunstan and Brown, Soc. 75, 72.
[19] Thoms and Wentzel, B. 31, 231.

in ether; its solubility in water is somewhat greater than that of atropine. Like this base its taste is sharp and penetrating and its physiological properties are the same as those of atropine. The chief difference between the two alkaloids lies in the optical activity of the hyoscyamine, which in contrast to the inactive atropine is strongly lævorotatory. According to Hesse the rotatory power decreases after the base has been kept for some time.

Dehydrating agents convert hyoscyamine into atropamine and belladonnine. These are identical with the alkaloids obtained from atropine by similar treatment.[20]

Hyoscyamine is saponified by baryta-water and by alkalies. Höhn and Reichardt,[21] who first observed this saponification in 1871, gave to the two decomposition-products obtained the names *hyoscic acid* and *hyoscine.* Ladenburg [22] showed later that hyoscic acid was identical with inactive tropic acid and hyoscine with tropine, and he obtained accordingly, by treating a mixture of the two with dilute hydrochloric acid, not hyoscyamine but atropine.

The explanation of this behavior was given by Merck [23] in 1883. By saponifying hyoscyamine with hot water, he obtained in addition to tropine an active, lævorotatory tropic acid. This lævo-tropic acid is the direct saponification-product of hyoscyamine; if the saponification, however, is conducted in an acid or alkaline solution, the active acid is converted into the racemic form. It is accordingly no longer surprising that this acid by its union with tropine forms atropine.

This observation appears to confirm the statement made on page 189, according to which hyoscyamine should be considered as the lævo-modification of atropine. An experiment made by Ladenburg and Hundt [24] in 1889, however, would seem to indicate

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[20] Hesse, A. **277**, 290; Schmidt, A. Pharm. **232**, 409.
[21] Höhn and Riechardt, A. **157**, 98.
[22] Ladenburg, B. **13**, 109, 254, 607; A. **206**, 286.
[23] Merck, A. Pharm. **231**, 115.
[24] Ladenburg and Hundt, B. **22**, 2590.

that the relation existing between the two alkaloids is not so simple as we might suppose. These investigators succeeded in separating inactive tropic acid through its quinine salt into the two active forms. The lævo-acid thus prepared should be identica with that obtained by Merck, since in tropic acid, as we shall see later, there is only *one* asymmetric carbon atom. Now Ladenburg and Hundt, on uniting this lævo-acid with inactive tropine, obtained a *lævo-atropine*, which although similar to hyoscyamine was apparently not identical with it. From this one might conclude that the stereoisomerism of the two alkaloids is not situated alone in the acid part of the molecule—the tropic acid—but also in the basic part—the tropine.

According to the investigations of Gadamer,* however, the tropine in both atropine and hyoscyamine is inactive and the only difference between the two alkaloids lies in the inactivity in one case and the activity in the other of the tropic acid radical. Recently Amenomiya † states that he has obtained *d*- and *l*-hyoscyamine by the union of *d*- and *l*-tropic acids with tropine.

3. Pseudohyoscyamine.

This alkaloid, as yet little studied, was obtained in 1892 by Merck [25] from *Duboisia myoporoides.* It crystallizes from a mixture of ether and chloroform in needles which melt at 133–134°; it is easily soluble in alcohol and chloroform, difficultly so in water and ether. Pseudohyoscyamine is lævorotatory; in physiological action it is little poisonous; like atropine, it causes dilation of the pupil.

When saponified with baryta-water, the alkaloid is converted into tropic acid and a base, $C_8H_{15}NO$, which is, however, different from tropine.

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* See note 7, p. 189.

† See note 8, p. 189.

[25] Merck, A. Pharm. 231, 115.

4. Hyoscine.

Ladenburg[26] gave this name to an alkaloid which he had isolated from the seed of the henbane in connection with hyoscyamine. It is said to be an isomer of the alkaloids just considered; in its physiological action, like atropine, it is mydriatic. The free base was obtained as a sirup-like mass and was converted into a crystalline gold salt melting at 198°.

Upon saponification with alkalies, hyoscine was decomposed into tropic acid and a base, $C_8H_{15}NO$, which differed from tropine and consequently received the name of *pseudotropine.*

Schmidt[27] believes that hyoscine is to be identified with *scopolamine,* $C_{17}H_{21}NO_4$, which is extracted from the roots of *Scopolia atropoides* (page 196), and Hesse[28] in accord with this declares that Ladenburg's hyoscine has the formula $C_{17}H_{21}NO_4$. According to Hesse, hyoscine may be converted into atroscine.[29]

Merck[30] in working up large quantities of the seed of the henbane was unable to obtain a product with properties and composition of Ladenburg's hyoscine.

Further investigations are needed to throw light upon these conflicting observations.

5. Atropamine.

Atropamine was extracted by Hesse[31] in 1891 from the roots of the belladonna. In his studies, which were at the same time taken up by Hesse and Merck,[32] it was soon shown that the base

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[26] Ladenburg, B. **13**, 910, 1549; **14**, 1870; **17**, 151; **20**, 1661; **25**, 2388; A. **206**, 299.

[27] Schmidt, B. **29**, 2009; A. Pharm. **230**, 693.

[28] Hesse, A. **271**, 100; **303**, 149; **309**, 75.

[29] Hesse, J. pr. [2] **64**, 353.

[30] Merck, J. Soc. Chem. Ind. **16**, 515.

[31] Hesse, A. **261**, 87; **271**, 100; **277**, 290.

[32] Merck, A. Pharm. **230**, 134; **231**, 110.

was identical with the apoatropine, $C_{17}H_{21}NO_2$, which Pesci[33] had already obtained by treating atropine with concentrated nitric acid.

Hesse and Schmidt showed, furthermore, that it is always this alkaloid that is formed from atropine, or hyoscyamine, when they are dehydrated with sulphuric acid, or the anhydrides of phosphoric acid, acetic acid, etc.

Atropamine crystallizes from ether in prisms which melt at 60°–62° and which are easily soluble in alcohol, ether, and chloroform, somewhat soluble in benzol, and little soluble in water and ligroin. Its taste is bitter and disagreeable; it possesses no mydriatic action, and has no effect upon polarized light.

The base is an unsaturated body, since on treatment with sodium amalgam it takes up two atoms of hydrogen and forms an oily base, $C_{17}H_{23}NO_2$, *hydro-atropine,* or *hydro-apoatropine.*

On being heated, atropamine undergoes a molecular rearrangement to form its isomer, belladonnine. Also when the base is warmed with barium hydroxide, or with hydrochloric acid, there first occurs this same rearrangement, but this is then followed by saponification to *atropic acid* and *tropine:*

$$\underset{\text{Atropamine}}{C_{17}H_{21}NO_2} + H_2O \rightarrow \underset{\text{Atropic acid}}{C_9H_8O_2} + \underset{\text{Tropine}}{C_8H_{15}NO}.$$

Ladenburg[34] succeeded in reversing this reaction; by heating on the water-bath a mixture of tropine and atropic acid with hydrochloric acid he obtained atropamine.

The alkaloid is consequently the tropeïne of atropic acid, just as atropine and hyoscyamine are the tropeïnes of tropic acid.

[33] Pesci, G. 11, 538; 12, 591, 285, 329.
[34] Ladenburg, A. 217, 290.

6. Belladonnine.

Kraut[35] was the first investigator who succeeded in isolating belladonnine in a condition of purity (1868). He assigned to it the formula $C_{17}H_{23}NO_3$, and consequently considered it as an isomer of atropine. Merling[36] and Hesse[37] showed later that its composition corresponded to the formula $C_{17}H_{21}NO_2$. It thus contains a molecule less of water than was at first supposed and it is consequently an isomer of atropamine.

It is found in small quantity in the belladonna (0.01–0.04%). Belladonnine is formed from its isomer, atropamine, when the latter is heated, or is treated with acids or barium hydroxide. It is further formed by the withdrawal of water from atropine when the latter is heated to 130°. Here, as we have already seen, atropamine is the first product of the reaction.[37, 38]

Belladonnine is separated as a resinous, yellow mass which is readily soluble in various organic solvents and but little soluble in water. On hydrolysis it is decomposed into the same derivatives as atropamine, viz., atropic acid and tropine. Probably these two alkaloids are stereoisomers.

7. Scopolamine (Atroscine).

In 1888 Schmidt[39] extracted from the roots of *Scopolia atropoides* Bercht. and those of *Scopolia japonica* Maxim. an alkaloid, $C_{17}H_{21}NO_4$, which he named scopolamine. It was later found also in other members of the family Solanaceæ.

Scopolamine crystallizes with one molecule of water and melts at 59°. It is lævorotatory, its hydrobromide having a

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[35] Kraut, A. **148**, 236; B. **13**, 165.

[36] Merling, B. **17**, 381.

[37] Hesse, A. **261**, 87; **271**, 100; **277**, 290.

[38] Merck, A. Pharm. **221**, 110.

[39] Schmidt, A. Pharm. **226**, 185; **228**, 435; **229**, 518; **230**, 207; **232**, 409; **236**, 47; B. **25**, 2601; **29**, 2009; *Apotheker-Zeitung*, **11**, 260, 321.

specific rotation of $-25° 43'$. In water it is little soluble, but it dissolves readily in organic solvents. It is a tertiary base and contains a methyl group attached to the nitrogen.[40]

By the action of concentrated sulphuric acid water is withdrawn from scopolamine and there is formed the derivative $C_{34}H_{40}N_2O_7$.

When the alkaloid is saponified with alkalies, barium hydroxide, or hydrochloric acid, it is decomposed into *tropic acid* and *scopoline:*

$$\underset{\text{Scopolamine}}{C_{17}H_{21}NO_4} + H_2O \rightarrow \underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Scopoline}}{C_8H_{13}NO_2}.$$

Scopolamine may then be characterized as *tropylscopoleïne.*

When the anhydride of tropic acid is heated with scopoline, there is obtained an *apo*-derivative, $C_{17}H_{19}NO_3$, which differs from scopolamine by containing one molecule less of water. In its salts this new base takes up water and forms derivatives which are isomeric with those of scopolamine.

Scopoline can be caused to unite with other acids, forming the scopoleïnes, such as *salicylscopoleïne,* $C_{15}H_{17}NO_4$, which is obtained by heating a mixture of scopoline and salicylide to 230°.[41]

By the action of alkalies or alkali carbonates scopolamine may be converted into an inactive crystalline derivative, *isoscopolamine,* $C_{17}H_{21}NO_4 + H_2O$ (melting-point 56°). This forming of an inactive derivative is denied by Hesse.

In commercial scopolamine hydrobromide Hesse[42] found an inactive alkaloid to which he gave the name of *atroscine,* $C_{17}H_{21}NO_4 + 2H_2O$ (melting-point 37–38°). Atroscine is also found in the roots of *Scopolia atropoides,* from which the commercial scopolamine hydrobromide is prepared.

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[40] Herzig and Meyer, M. **18**, 379.

[41] Luboldt, A. Pharm. **236**, 33.

[42] Hesse, A. **271**, 100; **276**, 84; **277**, 304; **303**, 149; **309**, 75; B. **29**, 1771; J. pr [2] **64**, 353; **66**, 194.

Now it appears that isoscopolamine and atroscine are closely related to each other;[48] they appear, indeed, to be hydrates of the same alkaloid; isoscopolamine crystallizes with one molecule of water, atroscine with two. The anhydrous alkaloid, $C_{17}H_{21}NO_4$, is crystalline, melts at 82°–83, and is best obtained by warming isoscopolamine to 54–55°.

In confirmation of this view we note that atroscine can be converted into isoscopolamine by inoculating an atroscine solution with a crystal of isoscopolamine; the reverse transformation is also effected under certain conditions by adding a crystal of atroscine to an isoscopolamine solution.

Further atroscine may be changed to isoscopolamine if the hydrobromide of the former is prepared, the base again freed from this and crystallized from an aqueous solution of definite concentration at 0°.

Both isoscopolamine and atroscine, like scopolamine itself, are decomposed by alkalies into tropic acid and scopoline.

In order that the relation of these various scopolamine derivatives to one another may be more clearly represented, Wolffenstein proposes the following nomenclature:

The inactive anhydrous alkaloid $C_{17}H_{21}NO_4$ = *i*-scopolamine;
The inactive alkaloid containing *one* molecule of water (isoscopolamine) = *i*-scopolamine monohydrate;
The inactive alkaloid containing *two* molecules of water (atroscine) = *i*-scopolamine dihydrate.

It is clearly seen from the preceding data that all the alkaloids of the Solanaceæ stand in close chemical relation to one another. In particular they are decomposed by hydrolysis into an acid containing nine carbon atoms and into a basic alcohol containing eight:

Atropine and hyoscyamine into tropic acid, $C_9H_{10}O_3$, and tropine, $C_8H_{15}NO$;

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[48] Gadamer, A. Pharm. **236**, 382; **239**, 294, 321; J. pr. [2] **64**, 565, 569.

Pseudohyoscyamine into tropic acid and a base, $C_8H_{15}NO$ (different from tropine);

Atropamine and belladonnine into atropic acid, $C_9H_8O_2$, and tropine;

Scopolamine into tropic acid and scopoline, $C_8H_{13}NO_2$.

It now remains for us to determine the constitution of these products of decomposition.

Atropic Acid $C_9H_8O_2$.—Atropic acid forms tabular crystals which melt at 106°.5; it boils with partial decomposition at 267°. It is an unsaturated, monobasic acid which will add two atoms of hydrogen, or bromine, or one molecule of a halogen acid. Chromic acid oxidizes it to benzoic acid and carbon dioxide; fused with caustic alkali it yields phenylacetic and formic acids.

According to its empirical formula atropic acid is an isomer of cinnamic acid. The relation existing between these two acids is shown in the following formulæ:

$$C_6H_5—CH{=}CH—COOH, \qquad C_6H_5—C\begin{cases}{=}CH_2\\ —COOH\end{cases}.$$

Cinnamic acid (β-phenylacrylic acid) Atropic acid (α-phenylacrylic acid)

This constitution of atropic acid is confirmed by its synthesis, which was effected by Ladenburg and Rügheimer [44] in 1880. This synthesis depends on the following reactions:

1. When acetophenone is heated with phosphorus pentachloride its oxygen is exchanged for two chlorine atoms and there is formed *dichlorethylbenzol:*

$$C_6H_5—CO—CH_3 + PCl_5 \rightarrow C_6H_5—CCl_2—CH_3 + POCl_3.$$

2. If this latter is treated with an alcoholic solution of potassium cyanide a double reaction occurs; one of the two chlorine atoms is replaced by the cyanogen radical, the other by the

[44] Ladenburg and Rügheimer, B. 13, 376, 2041; A. 217, 74.

ethoxyl group. There is thus obtained a nitrile which on saponification yields an acid:

$$C_6H_5\text{—}CCl_2\text{—}CH_3 + KCN + C_2H_5OH \rightarrow$$

$$C_6H_5\text{—}C\begin{matrix} \diagup CH_3 \\ \text{—}OC_2H_5 \\ \diagdown CN \end{matrix} + KCl + HCl;$$

$$C_6H_5\text{—}C\begin{matrix} \diagup CH_3 \\ \text{—}OC_2H_5 \\ \diagdown CN \end{matrix} + 2H_2O \rightarrow C_6H_5\text{—}C\begin{matrix} \diagup CH_3 \\ \text{—}OC_2H_5 \\ \diagdown COOH \end{matrix} + NH_3.$$

3. When the acid thus formed (*ethyl-α-phenyllactic acid*) is heated with concentrated hydrochloric acid, it loses a molecule of alcohol and is converted into *atropic acid:*

$$C_6H_5\text{—}C\begin{matrix} \diagup CH_3 \\ \text{—}OC_2H_5 \\ \diagdown COOH \end{matrix} \rightarrow C_6H_5\text{—}C\begin{matrix} /\!\!/ CH_2 \\ \\ \diagdown COOH \end{matrix} + C_2H_5OH.$$

Tropic Acid, $C_9H_{10}O_3$.—This acid crystallizes in prisms, or plates, melting at 117–118°. It is optically inactive and without any particular physiological action.

It is a saturated acid; it contains an alcoholic hydroxyl group which under the action of phosphorus pentachloride is easily exchanged for a chlorine atom. Dehydrating agents convert the acid into atropic acid. These facts enable us to assign to it one of the two following formulæ:

$$\underset{\text{I}}{C_6H_5\text{—}CH\begin{matrix} \diagup CH_2OH \\ \diagdown COOH \end{matrix}} \quad \text{or} \quad \underset{\text{II}}{C_6H_5\text{—}COH\begin{matrix} \diagup CH_3 \\ \diagdown COOH \end{matrix}}.$$

Now since 1879 there has been known an acid which is isomeric with tropic acid. Fittig and Wurster[45] obtained this isomer by heating with sodium carbonate the addition-product which

[45] Fittig and Wurster, A. 195, 153.

atropic acid forms with hydrogen bromide. The new acid received the name *atrolactic acid*. It crystallizes with a half-molecule of water and after being dried melts at 94°. Dehydrating agents convert it into atropic acid.

The constitution of atrolactic acid must consequently correspond with one of the above formulæ; if this can be determined, we will at the same time fix the constitution of tropic acid. Now two syntheses of atrolactic acid, which were published in 1881 almost simultaneously by Böttinger[46] and Spiegel,[47] show that the constitution of the acid is represented by formula II.

Böttinger found that dibrompyruvic acid and benzol in the presence of sulphuric acid form an addition-product, which is none other than dibromatrolactic acid. From this by reduction with sodium amalgam atrolactic acid itself is obtained:

$$C_6H_6 + CO\left\langle\begin{matrix}CHBr_2\\COOH\end{matrix}\right. \rightarrow C_6H_5\text{—}COH\left\langle\begin{matrix}CHBr_2\\COOH\end{matrix}\right.;$$

$$C_6H_5\text{—}COH\left\langle\begin{matrix}CHBr_2\\COOH\end{matrix}\right. + 4H \rightarrow C_6H_5\text{—}COH\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right. + 2HBr.$$

By treating acetophenone with prussic acid Spiegel prepared a cyanhydrine which proved to be the nitrile of atrolactic acid and on saponification was converted into that acid:

$$C_6H_5\text{—}CO\text{—}CH_3 + CNH \rightarrow C_6H_5\text{—}COH\left\langle\begin{matrix}CH_3\\CN\end{matrix}\right.;$$

$$C_6H_5\text{—}COH\left\langle\begin{matrix}CH_3\\CN\end{matrix}\right. + 2H_2O \rightarrow C_6H_5\text{—}COH\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right. + NH_3.$$

According to these two modes of preparing atrolactic acid, its constitution must be represented by formula II; that of its isomer, tropic acid, is accordingly given by formula I.

Tropic acid was synthesized in 1880 by Ladenburg and Rügheimer[48] from atropic acid. If the latter is treated with a

[46] Böttinger, B. 14, 1236.
[47] Spiegel, B. 14, 1353.
[48] Ladenburg and Rügheimer, B. 13, 376; A. 217, 74.

solution of hypochlorous acid, there is formed *chlortropic acid*. This then with a reducing agent (zinc-dust and caustic soda) yields tropic acid:

$$\underset{\text{Atropic acid}}{C_6H_5{-}C{<}{}^{CH_2}_{COOH}} + ClOH \rightarrow \underset{\text{Chlortropic acid}}{C_6H_5{-}CCl{<}{}^{CH_2OH}_{COOH}}$$

$$C_6H_5{-}CCl{<}{}^{CH_2OH}_{COOH} + 2H \rightarrow \underset{\text{Tropic acid}}{C_6H_5{-}CH{<}{}^{CH_2OH}_{COOH}} + HCl.$$

The formula of tropic acid contains an asymmetric carbon atom. It should be possible then to separate the inactive acid derived from atropine into two active modifications. This separation was effected by Ladenburg and Hundt [49] by crystallization of the quinine salt. *Dextro-tropic acid* melts at 127–128°, *lævo-tropic acid* at 123° (125–126°, Gadamer). The latter is probably identical with the lævo-acid which Merck [50] obtained by saponifying hyoscyamine with hot water (page 192).

Tropine, $C_8H_{15}NO$.—Tropine, the basic decomposition-product of the most of the solanum alkaloids, is a hygroscopic substance which crystallizes from ether in colorless plates and is easily soluble in water, alcohol, and ether. Tropine melts at 63° and boils without decomposition at 233°. It is a tertiary base, of strong alkaline reaction, without action on polarized light. It is much less poisonous than atropine and hyoscyamine, and it lacks the mydriatic properties of both these alkaloids.

When tropine is heated with sodium and amyl alcohol, it is converted into a stereoisomeric modification which is identical with pseudotropine, a base obtained by Liebermann from the saponification of one of the coca alkaloids (see Tropa-cocaine).[51]

For more than twenty years investigators have sought to gain a more satisfactory knowledge regarding the constitution of tropine. Of the investigations which have been undertaken

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[49] Ladenburg and Hundt, B. 22, 2590.
[50] Merck, A. Pharm. 231, 115.
[51] Willstätter, B. 29, 936.

there should be mentioned particularly those of Ladenburg,[52] Merling,[53] and Willstätter,[54] since they represent so many stages in the unfolding of the chemistry of tropine and atropine.

Ladenburg in a long series of important investigations determined the functions of the atomic complexes of tropine and presented these in a formula which we will consider farther on. The results obtained later by Merling led to a modification of this formula. Finally, through the observations of Willstätter the second formula in turn received a modification whose correctness has recently been confirmed by the synthesis of tropine.

We shall consider in chronological order the work of these three investigators.

Ladenburg showed first of all that tropine is an alcohol. With acids it easily forms esters, the so-called *tropeïnes* (see page 227); its oxygen atom is accordingly in a hydroxyl group. Tropine closely resembles the synthesized alcamines (see page 49).[55]

He further showed that tropine possesses a methyl group attached to the nitrogen. This is made clear by the following reactions:

When tropine is distilled with lime, soda-lime, or the oxide of barium it is decomposed, forming methylamine, some trimethylamine, and several hydrocarbons; among the latter are found a valerylene, C_5H_8, hydrocarbons of the formula $(C_6H_6)_x$, etc., and *tropilidene*, C_7H_8. The chief reaction which occurs may be expressed by the following equation:

$$\underset{\text{Tropine}}{C_8H_{15}NO} \rightarrow \underset{\text{Methylamine}}{CH_3NH_2} + \underset{\text{Tropilidene}}{C_7H_8} + H_2O.$$

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[52] Ladenburg, B. **12**, 942; **13**, 252; **14**, 227, 2126 2403; **15**, 1028, 1140; **16**, 1408; **17**, 157; **20**, 1647; **23**, 1780, 2225; **35**, 1159, 2295; A. **217**, 74.

[53] Merling, B. **14**, 1829; **15**, 288; **16**, 1238; **24**, 3108; **25**, 3123; A. **216**, 329.

[54] Willstätter, B. **29**, 393, 936, 1575, 1636, 2216, 2228; **30**, 731, 2679; **31**, 1534; **34**, 129, 3163; **35**, 1870; A. **317**, 204, 267, 307; **326**, 1, 23; Ber. dtsch. pharm. Ges. **13**, 50.

[55] Ladenburg, B. **14**, 1876, 2406; **22**, 2583.

A decomposition similar to this is effected by the destructive methylation of Hofmann. Tropine unites readily with a molecule of methyl iodide. The addition-product thus formed on treatment with moist silver oxide and subsequent distillation is decomposed into water and a new base, *α-methyltropine*, $C_9H_{17}NO$, an oily liquid boiling at 243°. This is also a tertiary base; it in turn will add a molecule of methyl iodide and the addition-product subjected to the above treatment suffers decomposition into water, trimethylamine, and *tropilidene.*

Tropilidene is a liquid insoluble in water and resembling toluol in odor. Its boiling-point is 117°; its specific gravity at 0°, 0.9129. Ladenburg did not determine the constitution of tropilidene, but from the formation of trimethylamine in the above reaction it naturally follows that tropine has a methyl group attached to the nitrogen.

Indeed trimethylamine could only result from the distillation of α-methyltropine methyl hydroxide in case the latter possessed three methyl groups attached to the nitrogen; consequently α-methyltropine must possess two and tropine itself one. The successive phases of these reactions will be rendered clear by the following equations:

$$\underset{\text{Tropine}}{C_7H_{12}O{=}N{-}CH_3} + CH_3I \rightarrow \underset{\text{Tropine methiodide}}{C_7H_{12}O{=}N\begin{cases}CH_3\\CH_3\\I\end{cases}};$$

$$\underset{\text{Tropine methyl hydroxide}}{C_7H_{12}O{=}N\begin{cases}CH_3\\CH_3\\OH\end{cases}} \rightarrow \underset{\text{α-Methyltropine}}{C_7H_{11}O{-}N\begin{cases}CH_3\\CH_3\end{cases}} + H_2O;$$

$$\underset{\text{α-Methyltropine methyl hydroxide}}{C_7H_{11}O{-}\underset{OH}{N}\begin{cases}CH_3\\CH_3\\CH_3\end{cases}} \rightarrow \underset{\text{Tropilidene}}{C_7H_8} + \underset{\text{Trimethlamine}}{N\begin{cases}CH_3\\CH_3\\CH_3\end{cases}} + 2H_2O.$$

In addition to the chief products, tropilidene and trimethylamine, there is obtained from the distillation of α-methyltropine

methyl hydroxide a small quantity of a body containing oxygen, the so-called *tropilene*, $C_7H_{10}O$. The formation of this substance is due to a secondary reaction, which may be expressed by the equation

$$C_7H_{10}O—N(CH_3)_3OH \rightarrow N(CH_3)_3 + C_7H_{10}O + H_2O.$$

Tropilene is a liquid almost insoluble in water. Its boiling-point is 186–188°, and its density at 0°, 1.0091. Its odor is like that of acetone, but reminds one at the same time of benzaldehyde.

Ladenburg attempted to synthesize α-methyltropine by uniting tropilene with dimethylamine. He thus obtained a body which, however, differed from α-methyltropine in its boiling-point (198–205°) and which he named *β-methyltropine.*

The existence of a *n*-methyl group in tropine has been shown in another way by Merling.[56] By the oxidation of tropine with an alkaline solution of potassium permanganate, there was formed a base of the formula $C_7H_{13}NO$, *tropigenine.* This crystallizes in needles which melt at 160°. It is a secondary base, and Merling concluded correctly that tropigenine owes its formation to the elimination of the methyl group attached to the nitrogen:

$$\underset{\text{Tropine}}{C_7H_{12}O{=}N—CH_3} \rightarrow \underset{\text{Tropigenine}}{C_7H_{12}O{=}N—H.}$$

Indeed, tropigenine will unite with a molecule of methyl iodide to form the hydriodide of tropine and with two molecules to form the methiodide of tropine.

Tropidine, $C_8H_{13}N$.—When tropine is heated at 150–180° with hydrochloric or hydriodic acid, or at 220° with sulphuric acid, it loses a molecule of water and is converted into *tropidine,* a base containing no oxygen:

$$\underset{\text{Tropine}}{C_8H_{15}NO} \rightarrow \underset{\text{Tropidine}}{C_8H_{13}N+H_2O.}$$

[56] Merling, B. 15, 289; A. 216, 329.

Tropidine is a liquid which boils at 162–163° and at 0° possesses a specific gravity of 0.9665. In odor it resembles conine and like this base it is more soluble in cold water than in hot; in alcohol it is readily soluble. It is a strong tertiary base. Tropidine is an unsaturated compound; it combines with the halogen halides, hypochlorous acid, etc. Under certain conditions in the presence of hydrobromic acid it will reunite with a molecule of water to form tropine. Potassium permanganate converts it, by the addition of two hydroxyls, into *dihydroxytropidine.*[57]

These reactions show that tropidine contains a double bond and that it is formed by the conversion of a group, $—CH_2—CHOH—$, into the ethylene group $—CH{=}CH—$.

Heated to a high temperature with hydriodic acid, tropidine yields a heptane boiling at 95°.[58]

By the elimination of its nitrogen atom, it gives rise to the same derivatives as tropine, viz., *tropilene* and *tropilidene.*

The former of these bodies is obtained by heating the methiodide of tropidine with caustic potash:

$$\underset{\text{Methyl iodide of tropidine}}{C_7H_{10}{=}N(CH_3)_2I} + KOH \rightarrow \underset{\text{Tropilene}}{C_7H_{10}O} + \underset{\text{Dimethylamine}}{(CH_3)_2NH} + KI.$$

When the corresponding methyl hydroxide of tropidine is distilled it does not yield tropilene, but a tertiary base, *methyltropidene.* This in turn changed to its methyl hydroxide is decomposed by heat into trimethylamine and tropilidene:

$$\underset{\text{Tropidine methyl hydroxide}}{C_7H_{10}{=}N(CH_3)_2OH} \rightarrow \underset{\text{Methyltropidine}}{C_7H_9—N(CH_3)_2} + H_2O;$$

$$\underset{\text{Methyltropidine methyl hydroxide}}{C_7H_9—N(CH_3)_3OH} \rightarrow \underset{\text{Tropilidene}}{C_7H_8} + N(CH_3)_3 + H_2O.$$

The hydrochloride of methyltropidine when heated to a high temperature undergoes rearrangement to the methyl chloride of tropidine.

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[57] Einhorn and L. Fischer, B. **26**, 2008.
[58] Hofmann, B. **16**, 586.

The study of the action of bromine on tropidine afforded Ladenburg the proof that this, and consequently also tropine and atropine, are derivatives of pyridine. The hydrobromide of tropidine gives first with bromine an addition-product, but when this is heated to 170–180° there ensues a complete decomposition of the molecule with the formation of hydrobromic acid, ethylene bromide, and a compound of the formula $C_6H_5Br_2N$, which Ladenburg called methyldibrompyridine:

$$C_8H_{13}N.HBr + 8Br \rightarrow C_6H_5Br_2N + C_2H_4Br_2 + 5HBr.$$

If a large excess of bromine is employed, there is obtained, instead of the last product, the *dibrompyridine* of Hofmann (see p. 15).

All these facts led Ladenburg to regard tropidine as a tetrahydro-derivative of pyridine in which the imide hydrogen is replaced by a methyl group and a hydrogen atom of the ring by a vinyl radical:

$$\underset{\text{Tropidine}}{CH_2{=}CH{-}C_5H_7{=}N{-}CH_3.}$$

What now is the position of the side-chain in the pyridine ring? An attempt was made to solve this question by studying hydrotropidine, the reduction-product of tropidine.

Hydrotropidine, $C_8H_{15}N$.—As an unsaturated body tropidine should apparently by the addition of two hydrogen atoms be converted into the saturated base $C_8H_{15}N$. The direct reduction of tropidine has, however, not been effected, but Ladenburg, starting from tropine, has succeeded indirectly in preparing the compound in question.

We saw that hydriodic acid at a temperature above 150° converts tropine by dehydration into tropidine. If the heating is conducted at a slightly lower temperature (140°), it is possible to isolate an intermediate product which Ladenburg improperly named *tropine iodide:*

$$\underset{\text{Tropine}}{C_8H_{15}NO} + 2HI \rightarrow \underset{\text{Tropine iodide}}{C_8H_{15}NI_2} + H_2O.$$

This derivative is the hydriodide of a base which is derived from tropine by exchanging its hydroxyl for an atom of iodine. When treated with moist silver oxide, however, tropine is not again formed, but an isomeric base, metatropine, a liquid boiling at 238°. The reduction of this tropine iodide with zinc and hydrochloric acid gave Ladenburg *hydrotropidine:*

$$\underset{\text{Tropine iodide}}{C_8H_{15}.NI_2} + 2H \rightarrow \underset{\text{Hydrotropidine}}{C_8H_{15}N} + 2HI.$$

Later Merling succeeded in obtaining this base from tropidine, but only by an indirect process. He formed first the addition-product of tropidine with hydrogen bromide and then reduced this with zinc and sulphuric acid.

Hydrotropidine is a liquid little soluble in cold water and still less so in hot. Its boiling-point is 167–169°, and its specific gravity at 0°, 0.9366.

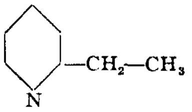
By dry distillation of its hydrochloride, hydrotropidine is decomposed into methyl chloride and a new base, $C_7H_{13}N$, called by Ladenburg *norhydrotropidine*. This is a solid with a melting-point of 60° and boiling-point of 161°; it is easily soluble in water, alcohol, and ether. It is not reducible either by tin and hydrochloric acid or by sodium and alcohol. Its properties are those of a secondary base; it is accordingly a hydrotropidine in which the *n*-methyl group has been replaced by a hydrogen atom:

$$\underset{\text{Hydrotropidine}}{C_7H_{12}{=}N{-}CH_3}, \qquad \underset{\text{Norhydrotropidine}}{C_7H_{12}{=}N{-}H}.$$

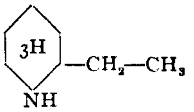
Ladenburg subjected the hydrochloride of norhydrotropidine to distillation over zinc-dust. The result of this treatment was quite analogous to that obtained by Hofmann in the case of conine (see pp. 127, 128). Hydrogen was evolved and there was formed a base of the pyridine series of the formula C_7H_9N. The properties of this base showed that it was *α-ethylpyridine* (see p. 37).

From these investigations Ladenburg decided that norhydro-

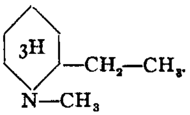
tropidine is a tetrahydro-α-ethylpyridine and that hydrotropidine is its *n*-methyl derivative, as represented in the following formulæ:



α-Ethylpyridine

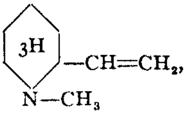


Norhydrotropidine



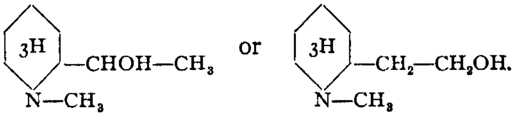
Hydrotropidine

From these formulæ there follows for tropidine, whose side-chain is a vinyl group, the following constitution:



Tropidine

and finally for tropine, which differs from tropidine by possessing the elements of a molecule of water, one of the two following formulæ:



Tropine

Such are the results of the long-continued investigations of Ladenburg. He sought to confirm his conclusions by synthesizing the bodies in question, but all his efforts in this direction led only to isomers (see p. 51).

Against the constitutional formulæ proposed by Ladenburg for tropine and its derivatives, it is possible *a priori* to raise several objections:

1. It seems strange that the moderate oxidation of tropine with potassium permanganate should affect the methyl group attached to the nitrogen (to form tropigenine) and should leave untouched the hydroxylated side-chain.

2. It is difficult to understand why tropidine, whose molecule according to Ladenburg contains a double bond lying outside

the ring, so resists the action of reducing agents, while α-allylpyridine, a body of analogous structure, readily adds hydrogen to form conine.

3. The fact that norhydrotropidine is a solid, while α-ethylpyridine and α-ethylpiperidine are mobile liquids, is not in accord with Ladenburg's formula, which represents norhydrotropidine as an α-ethylpiperideïne. Furthermore, a comparison of the boiling-points of the three derivatives leads to the same conclusion (α-ethylpyridine 148°.5, α-ethylpiperidine 142–145°, norhydrotropidine 161°).

There are other considerations which speak against the formulæ of Ladenburg. The following were noted in particular by Merling:

1. Tropine on oxidation yields a *di*basic acid. This important fact was also observed by Liebermann.[59] As we shall see, it is not compatible with the presence of only *one* side-chain in the molecule of tropine.

2. Tropine by simple reactions can be converted into derivatives of the aromatic series. Ladenburg's constitutional formulæ fail to explain such results.

We shall now consider more closely the work of Merling.

By the oxidation of tropine with chromic acid this investigator obtained an acid, $C_8H_{13}NO_4$, which he called *tropinic acid:*

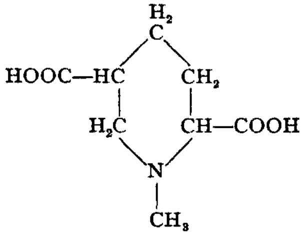
$$\underset{\text{Tropine}}{C_8H_{15}NO} + 4O \rightarrow \underset{\text{Tropinic acid}}{C_8H_{13}NO_4} + H_2O.$$

This acid, which is little soluble in cold water, alcohol, and ether, crystallizes from hot water or alcohol in needles. It melts at 248° and at the same time loses a molecule of carbon dioxide. On distillation with lime there was obtained a base which was easily soluble in water and which Merling regarded as a methylpiperidine, although he was unable definitely to establish its constitution.

Tropinic acid is optically inactive and possesses a methyl

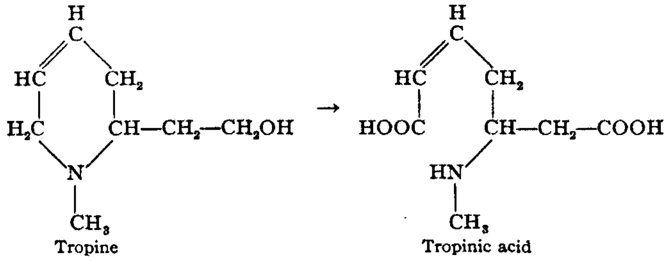
[59] Liebermann, B. 24, 606.

group attached to the nitrogen.[60] The study of its salts and esters has shown that it is a dibasic acid, $C_6H_{11}N(COOH)_2$. Merling regarded it as a *n*-methylpiperidine dicarboxylic acid and believed, for reasons which we will consider later, that the carboxyl groups occupied the $\alpha\beta'$ position:



The separation of tropinic acid into optically active constituents was effected by Gadamer [61] through the cinchonine salt. *l*-Tropinic acid melts with decomposition at 243°; its salts are dextrorotatory. The salts of *d*-tropinic acid on the contrary appear to be lævorotatory.

The formation of a dibasic acid by the oxidation of tropine Ladenburg [62] attempted to bring into agreement with his tropine formula by assuming a rupture of the pyridine ring in the following way:



The following observations of Willstätter [63] are, however, not in accord with this interpretation:

[60] Liebermann and Cybulski, B. 28, 584.
[61] Gadamer, A. Pharm. 239, 663.
[62] Ladenburg, B. 29, 421.
[63] Willstätter, B. 28, 2277, 3271.

1. Tropinic acid does not decolorize potassium permanganate in acid solution; it consequently does not contain an ethylene bond.

2. Its esters behave as tertiary bases.

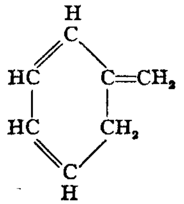
3. The methiodide of its dimethyl ester is decomposed by fusion with caustic potash, forming normal adipic acid.

4. The same methiodide, when it is subjected to the reaction of Hofmann, behaves exactly like piperidine (p. 29).

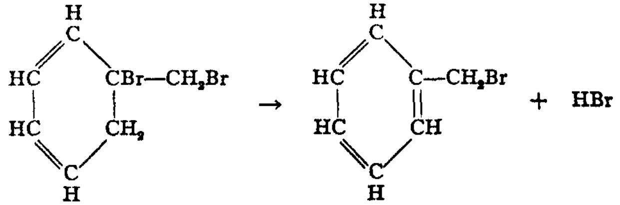
Since these results excluded Ladenburg's formula for tropinic acid, Merling considered it certain that the acid was *n*-methylpiperidine dicarboxylic acid. He accordingly now turned his attention to the study of tropilidene and tropilene.

Tropilidene, C_7H_8, an isomer of toluol, should possess a structure similar to that of this hydrocarbon, since on oxidation with chromic acid it yields a mixture of benzaldehyde and benzoic acid. With bromine it forms a dibromide, and when this is heated it is decomposed into hydrobromic acid and benzyl bromide.

These facts led Merling to assign to tropilidene the constitution of a *methylene dihydrobenzol:*

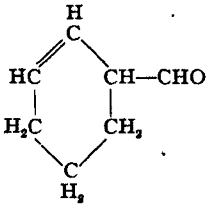


This formula explains very well the decomposition of dibromtropilidene into hydrobromic acid and benzyl bromide:



Dibromtropilidene Benzyl bromide

Also *tropilene*, $C_7H_{10}O$, according to Merling, would be an aromatic derivative, a *tetrahydrobenzaldehyde:*



This body possesses the properties of an aldehyde. It reduces Fehling's solution and an ammoniacal silver solution. It unites with the alkali bisulphites and reacts with hydroxylamine and phenylhydrazine. According to its molecular refractive power it possesses a double bond.[64] By oxidation, however, tropilene is not converted into benzoic acid; with permanganate it yields normal adipic acid.[65]

The question now naturally suggests itself whether the closed chain of six carbon atoms which is found in tropilidene and tropilene exists as such in tropine or whether it is formed only at the moment of decomposition by a sort of intramolecular condensation. Merling decided in favor of the former of these alternatives, which in his opinion alone afforded a satisfactory explanation of the formation of the dibasic tropinic acid.

We then obtain a formula which satisfies both conditions—the existence of a closed chain of six carbon atoms and the presence of two side-chains in the pyridine ring—when in Ladenburg's formula for tropine the second carbon atom of the oxyethyl group, instead of being at the free extremity of the open chain, is attached to the β'-carbon atom of the ring. This change necessitates another distribution of the hydrogen atoms in the tropine molecule; the piperideïne ring now becomes a piperidine nucleus.

Merling thus obtained, as an expression of the constitution of tropine, the two following schemes:

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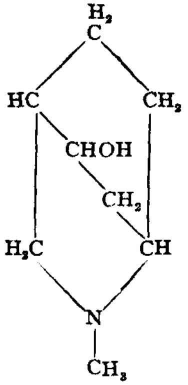
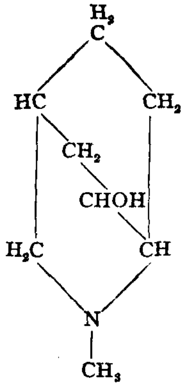
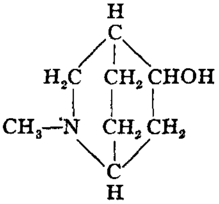
[64] Eykman, B. 25, 3069.
[65] Ciamician and Silber, B. 29, 481.



or



which may also be written as follows:



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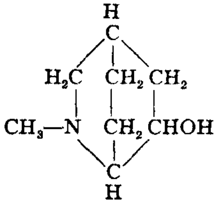
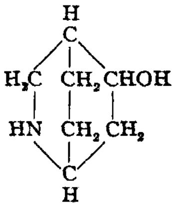


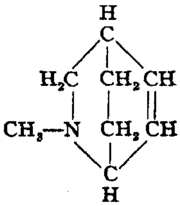
Tropine

In considering the above schemes we see that they are de-derived from a union of a benzol ring with a pyridine ring, both being completely reduced; there is thus formed an atomic grouping which reminds one of that of quinoline or isoquinoline. While in both these last derivatives, however, the pyridine and benzol rings have only two carbon atoms in common, here there are four.

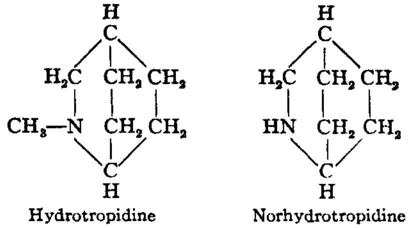
From this tropine formula of Merling's are derived for the immediate derivatives of tropine the following formulæ:



Tropigenine



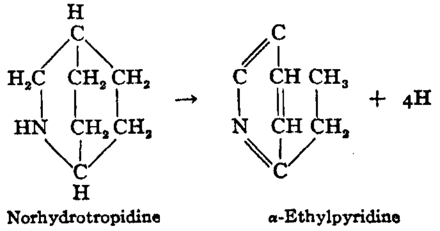
Tropidine



These formulæ make allowance for the chief properties of these bodies and their relations to one another just as well as the formulæ of Ladenburg. They, moreover, answer the objections which were raised against those of Ladenburg (see p. 209). They show why the hydroxyl group of the tropine is more resistant to oxidation than the methyl attached to the nitrogen, why tropidene is more difficult to reduce than allylpyridine, and why finally norhydrotropidine possesses melting- and boiling-points higher than those of ethylpyridine and ethylpiperidine.

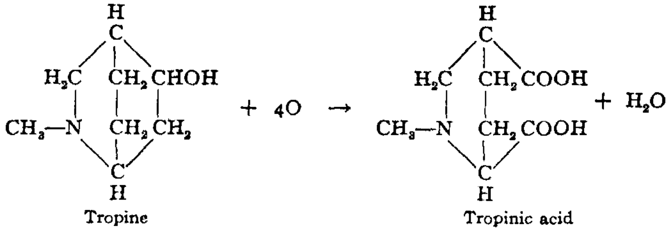
These formulæ also explain how tropine on oxidation can yield a dibasic, nitrogenous acid, and on elimination of the nitrogen may lead to the formation of hydroaromatic derivatives. In the decomposition of tropine and its derivatives it is in one case the piperidine, in another case the hydrobenzol nucleus which is destroyed, and that which remains gives to the product its aromatic or pyridic character.

Thus the formation of α-ethylpyridine by the distillation of norhydrotropidine over zinc-dust is explained by the rupture of the hydrobenzol ring:

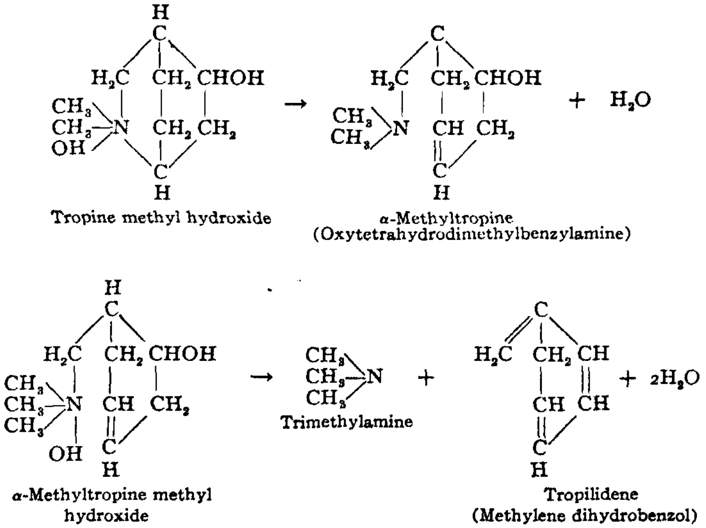


In the oxidation of tropine with chromic acid it is likewise the hydroaromatic nucleus which proves to be the more unstable;

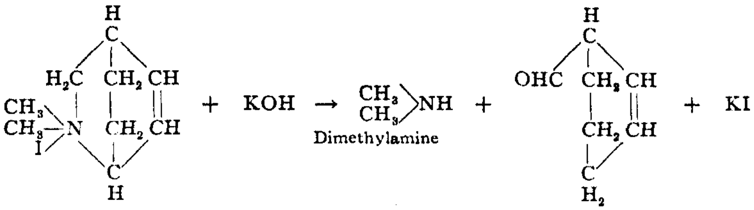
it is ruptured between the carbinol and the adjacent methylene group, which are then converted into two carboxyls. Thus there is obtained *n*-methyl-$\alpha\beta'$-piperidine carboxylic acid or tropinic acid:



In other cases, on the contrary, it is the piperidine nucleus which is broken and there are formed hydroaromatic derivatives. Thus, for example, the decomposition of tropine by the destructive process of Hofmann may be represented by the following equations:

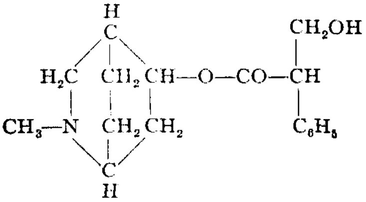


The formation of tropilene from the methiodide of tropidine by the action of caustic potash is explained in a similar way:

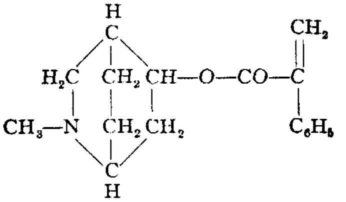


Tropidine methiodide — Tropilene (Tetrahydrobenzaldehyde)

The natural alkaloids which are the esters of tropine receive finally the following constitutional formulæ:



Atropine and Hyoscyamine



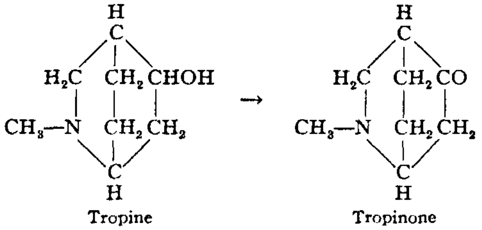
Atropamine and Belladonnine

Tropinone, $C_8H_{13}NO$.—For some time there has been known an oxidation-product of tropine lying between tropine and tropinic acid. This was obtained in 1896 almost simultaneously by Willstätter and by Ciamician and Silver and received from the first of these investigators the name of *tropinone.*

Tropinone is formed by the action of chromic acid, potassium permanganate, or lead peroxide on tropine. Willstätter also obtained it by treating the pseudotropine of Liebermann with chromic acid (see Tropa-cocaïne). On the other hand, when tropinone is reduced with sodium amalgam or sodium and

alcohol, it yields pseudotropine and not tropine; by *electrolytic* reduction, or reduction with zinc-dust and hydriodic acid, however, it is converted into tropine.

Tropinone is a solid which crystallizes from ligroin in needles, melts at 42°, and distils without decomposition at 224–225°. It is quite easily soluble in water and in the ordinary organic solvents; chromic acid oxidizes it to tropinic acid. Tropinone contains two hydrogen atoms less than tropine; it forms with hydroxylamine an oxime, with phenylhydrazine a hydrazone; in short, it is derived from tropine by the conversion of the CHOH group into a CO group:



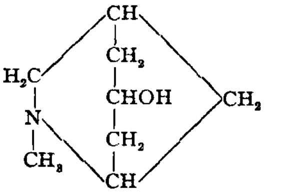
In a way analogous to that by which tropinone is obtained from tropine, there is formed from tropigenine, *nortropinone*, $C_7H_{11}NO$, a secondary base with the reactions of a ketone. Nortropinone crystallizes in needles melting at 69–70°. It cannot be distilled without decomposition. On reduction with sodium and alcohol it yields *pseudotropigenine.*

Tropinone is accordingly a ketone. Willstätter made this derivative with its reactive atomic grouping the starting-point of his investigations, instead of the more indifferent alcohol, tropine. He thus developed a modification of the tropine formula of Merling and succeeded fortunately in presenting the correct expression for the constitution of the tropine derivatives.

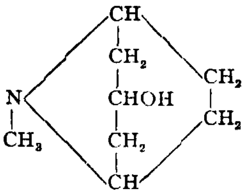
Willstätter found that the ketone group in tropinone stands between two CH_2 groups and is not, as Merling's formula represents it, adjacent to only *one* CH_2 group. He proved this by showing that tropinone gives with nitrous acid a diisonitroso-derivative and with benzaldehyde a dibenzal-product, that it

reacts with diazobenzol chloride, two radicals of phenylhydrazine being introduced, and that finally it reacts with oxalic ester to form mono- and di-oxalic esters.

According to these investigations there remains for tropine only one of the three following formulæ:

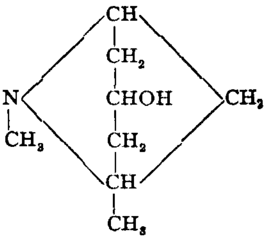


I



Tropine

II

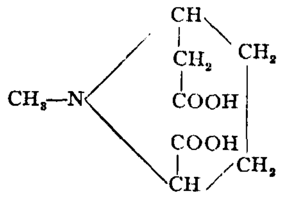


III

The choice between these three was determined by Willstätter by showing that tropine and its derivatives possess an unbranched chain of seven carbon atoms This condition is fulfilled only by formula II.

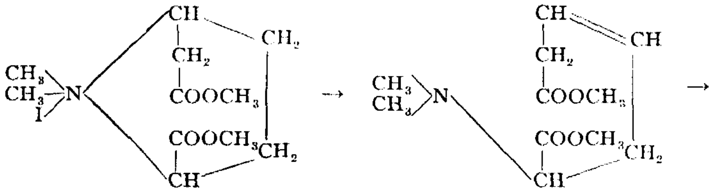
By exhaustive methylation of tropinic acid he obtained a diolefine dicarboxylic acid, which, on reduction with sodium amalgam in alkaline solution, yielded normal pimelic acid. From this it follows that tropinic acid itself must also have an unbranched chain of seven carbon atoms.

The constitution of tropinic acid should accordingly be represented as follows,

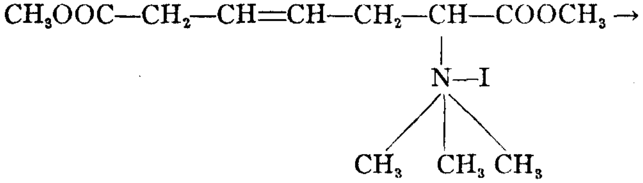


Tropinic acid

and the decomposition of tropinic acid to pimelic may be expressed in the following way:



Methyl iodide of tropinic ester   Methyltropinic ester



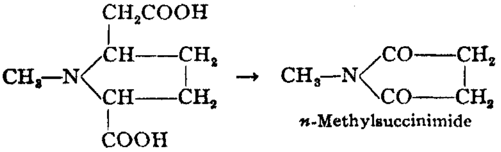
Methyl iodide of methyl tropinic ester

$$HOOC—CH_2—CH{=}CH—CH{=}CH—COOH \rightarrow$$

$$HOOC—CH_2—CH_2—CH_2—CH_2—CH_2—COOH.$$

Pimelic acid

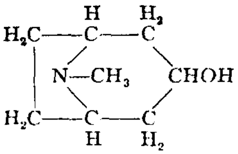
Tropinic acid appears thus to be a derivative of *n*-methylpyrrolidine. Willstätter has recently confirmed this by oxidizing the acid by means of chromic acid to *n-methylsuccinimide:*



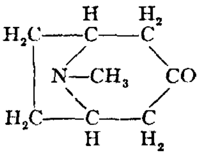
Tropinic acid   *n*-Methylsuccinimide

Tropine and its derivatives then appear to be derivatives of *cycloheptane*, in which there is a nitrogen atom joining two carbon atoms. Tropine thus presents a ring system which contains the piperidine, pyrrolidine, and heptamethylene nucleï somewhat oddly united.

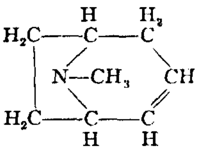
We have accordingly the following formulæ:



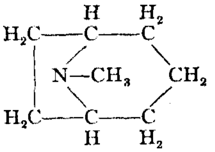
Tropine and Pseudotropine
(Tropanol)



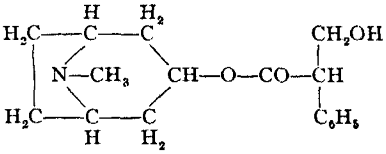
Tropinone
(Tropanone)



Tropidine
(Tropene)



Hydrotropidine
(Tropane)

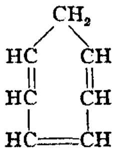


Atropine and Hyoscyamine

The names in parentheses are those suggested by Willstätter.

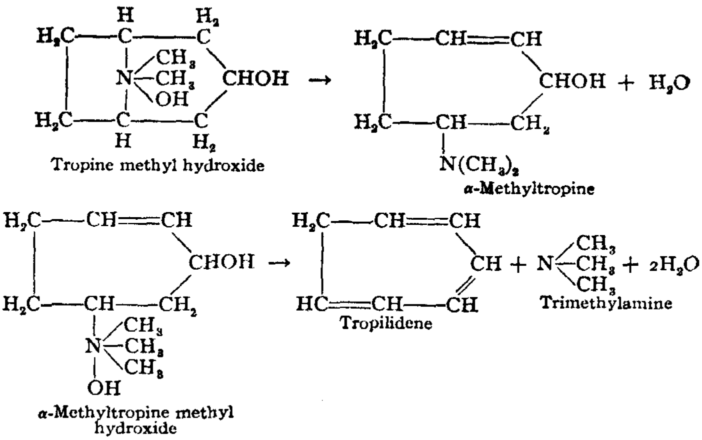
In closest harmony with these formulæ are all the reactions of tropine which have been discussed, particularly the formation of the derivatives free from nitrogen.

Thus *tropilidene*, C_7H_8, which is obtained in the exhaustive methylation of tropidine and tropine, is a cycloheptatriëne:

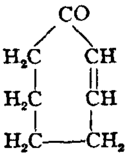


Tropilidene

The formation of this body may be made clear by the following formulæ:

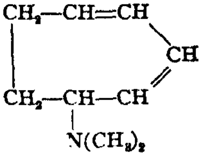


In the above reactions the *tropilene*, $C_7H_{10}O$, which is formed in small quantity with the tropilidene (see p. 204), Willstätter did not regard as an aldehyde, as it had been considered, but as a ketone, *cycloheptenone* ($\Delta^{\alpha\beta}$):

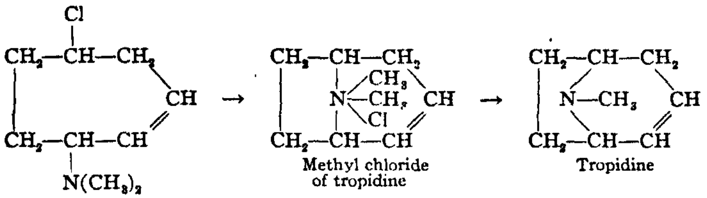

Tropilene

The ketone nature of tropilene is shown by its behavior. It forms with benzaldehyde a benzal compound, yields an oxymethylene derivative, and cannot be oxidized to an acid.

The Synthesis of Tropine.—A partial synthesis of tropidine from one of its decomposition-products has been known since 1889. This starts from the derivative then regarded as dihydroxybenzyldimethylamine, but which is now recognized as *dimethylamidocycloheptadiëne:*



This substance forms with hydrogen chloride an addition-product, which when heated yields the methyl chloride of tropidine. On distillation the latter is decomposed into methyl chloride and tropidine:

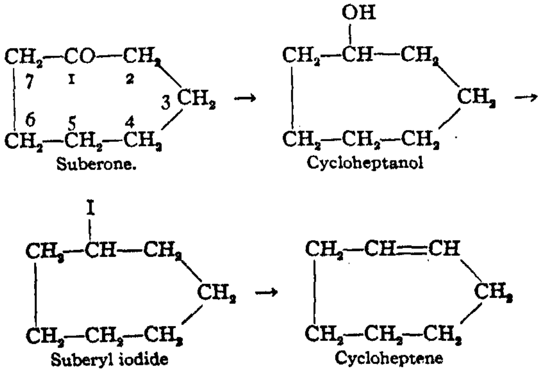


When this tropidine was heated with caustic alkalies, it is stated that tropine was formed.

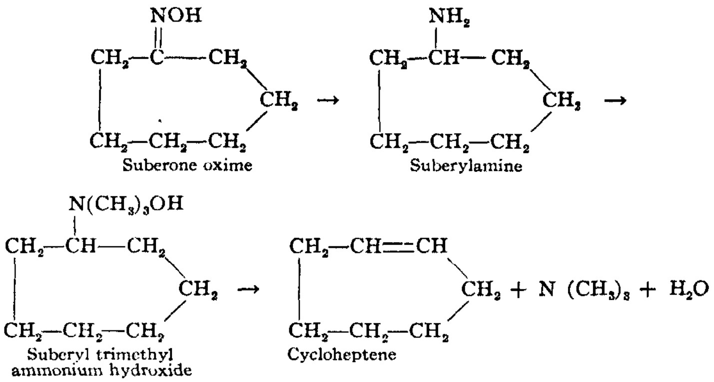
The complete synthesis of tropine has been effected by Willstätter within the last three years. The importance of this synthesis will be apparent when we see that it leads to that not only of atropine, atropamine, and belladonnine, but also of the coca alkaloids, tropa-cocaïne, and inactive cocaïne.

Willstätter started with suberone or cycloheptanone, which is formed by the distillation of the calcium salt of suberic acid. The various steps in the synthesis may be represented as follows:

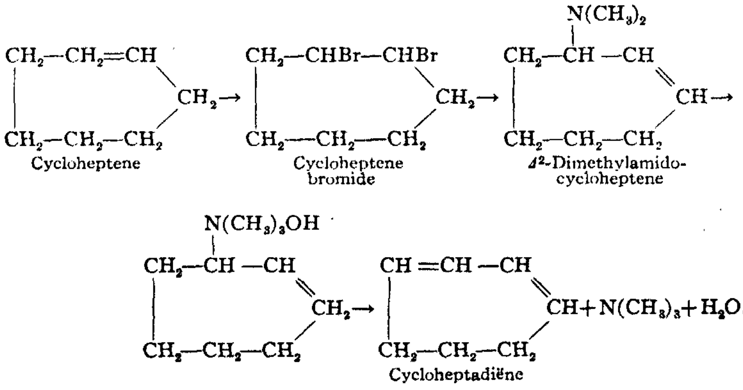
1. *From Suberone to Cycloheptene.*—This change is brought about in two ways: either by reduction to the alcohol, formation of the iodide and elimination of hydrogen iodide with alcoholic potash,



or by reduction of the oxime and exhaustive methylation of the resulting amine:



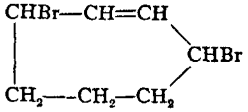
2. *From Cycloheptene to Cycloheptadiëne.*—With bromine cycloheptene yields a dibromide, which when heated with dimethylamine forms Δ^2-dimethylamidocycloheptene (Δ^2-methyltropane). If this last derivative is now completely methylated and the hydroxide distilled, *cycloheptadiëne* is obtained:



3. *Cycloheptadiëne to Cycloheptatriëne* (Tropilidene).—With one molecule of bromine cycloheptadiëne gives a dibromide. From the investigations of Thiele[66] concerning 1,4-addition-

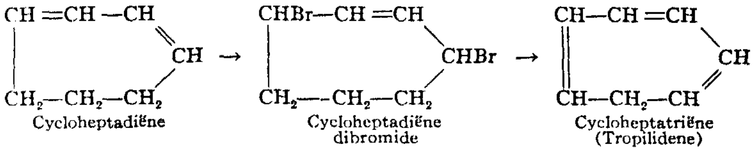
[66] Thiele, A. 306, 87; 308 333.

products, particularly with reference to the dibromides of butadiëne and cyclopentadiëne, it seems probable that the constitution of this dibromide should be represented as



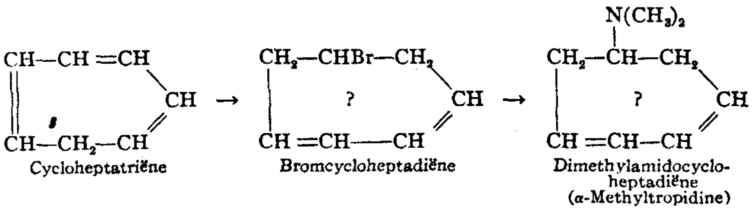
The behavior of the body towards different reagents fully accords with this supposition.

The conversion of the dibromide to *cycloheptatriëne* was effected most readily by heating it with quinoline to 150–165°:



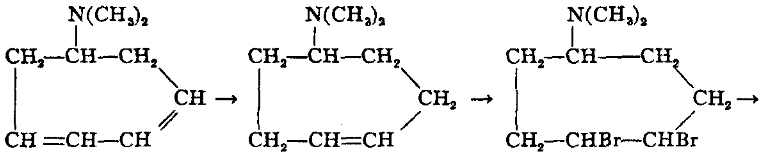
The tropilidene thus obtained was identical with that derived from tropine (p. 204).

4. *Tropilidene to Dimethylamidocycloheptadiëne* (α-Methyltropidine).—Cycloheptatriëne, when treated in the cold with one molecule of hydrogen bromide in glacial acetic acid, forms a monohydrobromide. By the action of dimethylamine, this addition-product is converted into *dimethylamidocycloheptadiëne.* Willstätter represents the change as follows:

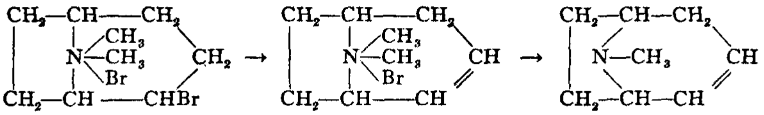


5. *α-Methyltropidine to Tropidine.*—On reduction with sodium and alcohol, α-methyltropidine readily takes up two atoms

of hydrogen to form a dimethylamidocycloheptene. When treated with bromine in a solution of hydrobromic acid, this last derivative yields a dibromide, which during the process of purification undergoes molecular rearrangement to a methyl bromide of bromtropane. Warming this bromide with a solution of caustic soda suffices to eliminate a molecule of hydrogen bromide and on addition of potassium iodide there is precipitated the methyl iodide of tropidine. If the iodide is now changed to the chloride by treatment with silver chloride and the latter is then heated, it is decomposed into methyl chloride and *tropidine:*



α-Methyltropidine — Δ^4-Dimethylamidocycloheptene — Bromide of the Δ^4-base



Methyl bromide of bromtropane — Methyl bromide of tropidine — Tropidine

The tropidine thus synthesized is in all respects identical with that obtained from tropine.

6. *Tropidine to Tropine.*—According to Ladenburg the direct conversion of tropidine to tropine by the action of hydrobromic acid was effected by himself as early as 1890. This result, at first doubted by Willstätter, has been confirmed by Ladenburg.[67]

Willstätter has further synthesized tropine from tropidine by heating tropidine hydrobromide with dilute sulphuric acid to 200–210°. There is thus first obtained pseudotropine (p. 252), which, on oxidation to tropinone and reduction of the latter with zinc-dust and hydriodic acid, is converted into tropine:[68]

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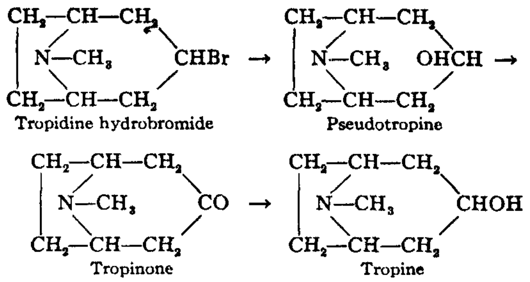
[67] Ladenburg, B. 23, 1780, 2225; 35, 1159, 2295.

[68] Willstätter and Iglauer, B. 33, 1170.



The synthesis of tropine from suberone presents the last step in the complete synthesis of the solanum alkaloids, atropine, atropamine, and belladonnine, and thus brings to a brilliant conclusion the extensive investigations of Ladenburg, Merling, and Willstätter regarding the constitution of these alkaloids:

Tropeïnes.—After having effected the synthesis of atropine by the union of tropine and tropic acid through the action of dilute hydrochloric acid, Ladenburg [69] replaced in this reaction the tropic acid with other aromatic acids. He thus obtained a series of esters which in their constitution are analogous to atropine and which he called *tropeïnes*. Such tropeïnes were later prepared by other investigators, particularly by Merck,[70] who extended the reaction to the acids of the fatty series.

The tropeïnes are crystalline bodies of basic character; some resemble atropine in their physiological action. We will enumerate below the most interesting of these derivatives:

1. *Benzoyltropeïne*, $C_8H_{14}N—O—CO—C_6H_5$, leaflets, melting at 41–42°, poisonous, but without mydriatic action.

2. *Salicyltropeïne*, $C_8H_{14}N—O—CO—C_6H_4—OH$, leaflets which melt at 58–60° and are without mydriatic action.

3. *Oxytoluyltropeïne*, $C_8H_{14}N—O—CO—CHOH—C_6H_5$ (Homatropine). This ester crystallizes in prisms melting at 95–98°. Homatropine is employed pharmaceutically instead of atropine, since its action on the pupil is almost as energetic as that of the natural alkaloid and has the advantage of disappearing

[69] Ladenburg, B. **13**, 106, 1080, 1137, 1549; **15**, 1025; **22**, 2590; A. **217**, 74.
[70] Merck, Bl. [3], **14**, 837.

more rapidly (in 12–24 hours; the action of atropine continues for about 8 days). Homatropine is also much less poisonous than atropine.

4. *Cinnamyltropeïne,* $C_8H_{14}N{-}O{-}CO{-}CH{=}CH{-}C_6H_5$, leaflets, melting at 70°, very poisonous, but without mydriatic action.

5. *Atropyltropeïne,* $C_8H_{14}N{-}O{-}CO{-}\underset{\substack{\| \\ CH_2}}{C}{-}C_6H_5$, identical with atropamine; does not dilate the pupil.

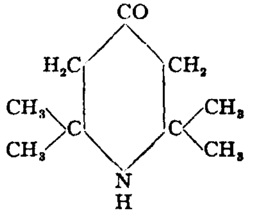
6. *Atrolactyltropeïne,* $C_8H_{14}N{-}O{-}CO{-}\underset{\substack{| \\ CH_3}}{C}(OH){-}C_6H_5$ (pseudoatropine), needles, melting at 119–120°, mydriatic in action.

7. *Lactyltropeïne,* $C_8H_{14}N{-}O{-}CO{-}CHOH{-}CH_3$, needles, melting at 74°–75°, affects the respiration and action of the heart.

It is noteworthy that all the tropeïnes which are mydriatic in action contain an alcoholic hydroxyl, while those possessing no hydroxyl, or at the most a phenol group, are without action on the pupil.

Attempts have been made also to prepare tropeïnes which instead of the tropine nucleus would contain synthesized rings of similar constitution. Esters have been thus prepared which possess mydriatic properties.

As a starting substance there has been employed here *triacetone amine,* which Heinz[71] obtained from acetone and ammonia:



The relation between triacetone amine and the tropine bases

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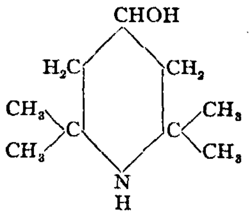
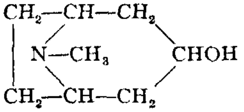
[71] Heinz, A. **189**, 214; **191**, 124; **198**, 69.

was shown by Fischer,[72] who first reduced the base to *triacetone alcamine*,

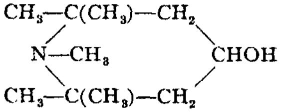


and then introduced a methyl group in place of the imide hydrogen.

The *triacetone methyl alcamine* thus obtained forms crystals melting at 74° and shows a close resemblance to tropine:



Tropine



Triacetone methyl alcamine

Its ester with mandelic acid is the analogue of homatropine and shows marked mydriatic properties.

Also a lower homologue of triacetone amine, *vinyl diacetone amine*, obtained by the interaction of diacetone amine and acetaldehyde has been used like triacetone amine in the synthesis of "tropeïnes." [73]

In preparing the *n*-methyl-vinyldiacetone amine, there are formed two stereoisomers, one, the α-, melting at 137–138°, the other, the β-alcamine, melting at 160–161°. The existence of these two stereoisomers is explained by the presence of the two asymmetric carbon atoms in the ring.[74]

When these isomers are converted into their esters with mandelic acid, only one, the β-alcamine, yields a derivative with mydriatic properties.

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[72] Fischer, B. **16**, 1604, 2236; **17**, 1797.

[73] Harries, A. **294**, 336; **296**, 328.

[74] Levy and Wolffenstein, B. **29**, 1959. Marcuse and Wolffenstein, B. **32**, 2525.

β-Oxytoluyl-n-methyl-vinyldiacetone alcamine, $C_9H_{18}N—O—CO—CHOH—C_6H_5$ (euphthalmine[75]) forms prisms which melt at 113°; its isomer, *α-oxytoluyl-n-methyl-vinyldiacetone alcamine*, is a viscid oil.

Pseudotropine, $C_8H_{15}NO$.—This isomer of tropine forms, according to Ladenburg,[76] the basic product resulting from the saponification of hyoscine. It occurs in crystals which melt at 106°; it boils at 242°. It is quite soluble in water, is less hygroscopic than tropine, and possesses the character of a tertiary base. In constitution it must be like tropine, but as yet we do not know in what the isomerism of the two bases consists.

This pseudotropine of Ladenburg should not be confused with that of Liebermann which the latter investigator obtained from the saponification of tropa-cocaïne, a coca alkaloid. These alkaloids, which were formerly supposed to be the same, are not identical.

Scopoline, $C_8H_{13}NO_2$.—Scopoline is the basic decomposition-product of scopolamine (atroscine). It was first obtained by Schmidt. Hesse, who prepared it from the so-called atroscine, named it *oscine.*

Scopoline crystallizes from ligroin or chloroform in prisms which melt at 110°. It is easily soluble in water and alcohol, little soluble in ether. It is a tertiary base and optically inactive. Scopoline possesses a methyl group attached to the nitrogen. Oxidized with potassium or barium permanganate, it is converted into a secondary base, *scopoligenine*, $C_7H_{11}NO_2$. This with methyl iodide is reconverted with scopoline.

Heated with concentrated hydriodic acid to 150°, scopoline is largely converted into a hydriodide of *hydriodoscopoline*, $C_8H_{14}O_2NI.HI$. On reduction with hydriodic acid and red phosphorus at a still higher temperature, scopoline yields *hydroscopolidine*, $C_8H_{15}N$.[77]

Of the two oxygen atoms in scopoline, one is probably ketonic

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[75] Harries, B. 31, 665.
[76] Ladenburg, B. 13, 1549; 14, 1870; 17, 151; 25, 2388; A. 276, 345.
[77] Schmidt, *Apoth.-Zeitung*, 17, 592.

in character, the other behaves as hydroxyl oxygen. The hydroxyl group reacts with organic acids in the presence of hydrochloric acid to form esters, the *scopoleïnes*, analogues of the tropeïnes.[78] Schmidt and Luboldt[79] prepared these scopoleïnes also by the action of various acid anhydrides on scopoline. In comparing the empirical formulæ of scopoline, $C_8H_{13}NO_2$, and of tropine, $C_8H_{15}NO$, it would appear that the former of the two bases was derived from the latter by the change of a CH_2 group to a CO group. According to the investigations of Schmidt and Luboldt this appears to be the case.

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[78] Merck, B. **28**, Ref. 520.

[79] Schmidt and Luboldt, A. Pharm., **236**, 11, 33.

CHAPTER XXII.

THE COCA ALKALOIDS.

THE leaves of *Erythroxylon Coca* Lam. (family of the Linaceæ) contain a number of alkaloids almost all of which bear a close chemical relation to one another. Thus far there have been isolated the following:

1. Cocaïne................ $C_{17}H_{21}NO_4$
2. Cinnamylcocaïne........ $C_{19}H_{23}NO_4$
3. α-Truxilline............ $(C_{19}H_{23}NO_4)_2$
4. β-Truxilline............ $(C_{19}H_{23}NO_4)_2$
5. Benzoylecgonine........ $C_{16}H_{19}NO_2$
6. Tropa-cocaïne.......... $C_{15}H_{19}NO_2$
7. Hygrine................ $C_8H_{15}NO$
8. Cuscohygrine........... $C_{13}H_{24}NO_2$

Günther[1] has discovered a methylcocaïne, $C_{18}H_{23}NO_4$, but further data are desired regarding this compound.

The first four alkaloids are by far the most abundant and are found in all the varieties of coca. The coca alkaloids, called also *cocaïnes*, are all esters of the same substance, *ecgonine*. On saponification with alkalies or acids, the cocaïnes are decomposed into ecgonine, methyl alcohol, and an aromatic acid. The acid varies in its composition in different cases, while the first two compounds remain the same; Günther's coca alkaloid, however, appears to yield ethyl alcohol as a product of decomposition. Cocaïne contains benzoic acid; cinnamylcocaïne, cinnamic acid; and the truxillines, two isomeric truxillic acids.

When the crude mixture of the alkaloids, as it is extracted directly from the plant, is saponified, there are obtained also

[1] Günther, *Berichte der deutschen pharmaceutischen Gesellschaft*, 9, 38.

other acids (*isocinnamic, allocinnamic, homococaïc, homoisococaïc acids*). From the occurrence of these acids we naturally conclude that the corresponding cocaïnes exist in the coca-leaves; as yet, however, these cocaïnes have not been isolated.

Of all the cocaïnes, the first only, cocaïne itself, is crystalline and possesses a therapeutic value; the others are amorphous and without special physiological action.

1. COCAÏNE.

Cocaïne, which was isolated by Niemann[2] in 1860, possesses the formula $C_{17}H_{21}NO_4$.[3] It is found in the coca-leaves only in small quantities (at the most 1%).

It crystallizes from alcohol in prisms which melt at 98°. In water it is little soluble. Its solutions taste bitter, react alkaline, and are lævorotatory; the hydrochloride in aqueous solution shows a specific rotation of $-71°.95$.[4] It is used in medicine as a local anesthetic, ordinarily in the form of its hydrochloride.

Cocaïne is a tertiary base. It contains a methoxyl and a *n*-methyl group.[5]

It is an ester; even boiling with water is sufficient to saponify it; it is thus decomposed into *benzoylecgonine* and methyl alcohol:[6]

$$\underset{\text{Cocaïne}}{C_{17}H_{21}NO_4} + H_2O \rightarrow \underset{\text{Benzoylecgonine}}{C_{16}H_{19}NO_4} + \underset{\text{Methyl alcohol}}{CH_3OH}.$$

If in this reaction the water is replaced by mineral acids, baryta-water, or caustic alkalies, the benzoylecgonine is also decomposed and there are formed ecgonine, benzoic acid, and methyl alcohol:[7]

$$\underset{\text{Cocaïne}}{C_{17}H_{21}NO_4} + 2H_2O \rightarrow \underset{\text{Ecgonine}}{C_9H_{15}NO_3} + \underset{\text{Benzoic acid}}{C_7H_6O_2} + \underset{\text{Methyl alcohol}}{CH_3OH}.$$

[2] Niemann, A. 114, 213.
[3] Lossen, A. 133, 351.
[4] Hérissey, J. Ph. chm. [6], 7, 59.
[5] Herzig and Meyer, B. 27, 319; M. 15, 613.
[6] Paul, *Pharmaceutical Journal*, 3, 325. Einhorn, B. 21, 47.
[7] Lossen, A. 133, 351. Calmels and Gossin, C. r. 100, 143.

Cocaïne is accordingly an ecgonine in which one hydrogen atom is replaced by a benzoyl group and another by a methyl group:

Ecgonine........................	$C_9H_{15}NO_3$
Benzoylecgonine..................	$C_9H_{14}NO_3(COC_6H_5)$
Cocaïne (Methylbenzoylecgonine).....	$C_9H_{13}NO_3(COC_6H_5)(CH_3)$

Cocaïne may be synthesized from ecgonine in several ways. Merck[8] and Skraup[9] in 1885 first prepared it artificially by heating benzoylecgonine with methyl iodide:

$$\underset{\text{Benzoylecgonine}}{C_{16}H_{19}NO_4} + CH_3I \rightarrow \underset{\text{Hydriodide of cocaïne}}{C_{17}H_{21}NO_4HI}.$$

Merck[10] then succeeded in converting ecgonine into cocaïne in one operation by heating it with benzoic anhydride and methyl iodide for ten hours in a closed tube at 100°:

$$2\underset{\text{Ecgonine}}{C_9H_{15}NO_3} + \underset{\text{Benzoic anhydride}}{(C_7H_5O)_2O} + 2CH_3I \rightarrow$$

$$\underset{\text{Hydriodide of cocaïne}}{C_{17}H_{21}NO_4HI} + \underset{\text{Hydriodide of ecgonine}}{C_9H_{15}NO_3HI} + \underset{\text{Methyl benzoate}}{C_7H_5O_2CH_3}.$$

These methods of preparing cocaïne afforded, however, only a small yield of the alkaloid and it remained for Liebermann[11] to develop a more productive method of synthesis. By the action of benzoic anhydride on ecgonine in concentrated aqueous solution he obtained benzoylecgonine. This treated with hydrogen chloride or sulphuric acid in a solution of methyl alcohol yielded cocaïne.

This process is used to-day commercially to convert into cocaïne all the coca alkaloids. We have seen that of all these alkaloids, cocaïne is the only one of pharmaceutical value. Its

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[8] Merck, B. 18, 2264.
[9] Skraup, M. 6, 556.
[10] Merck, B. 18, 2952.
[11] Libermann, B. 21, 3196; 27, 2051.

separation from the others is difficult. It is preferable to withdraw from the mixture by saponification all the ecgonine and then to convert this into cocaïne. There is thus secured a larger quantity of pure cocaïne than was originally present in the plant.

Einhorn [12] also prepared cocaïne by first methylating ecgonine and then heating with benzoyl chloride the methyl ester of ecgonine thus obtained.

If in the preceding reactions the methyl alcohol is replaced by other alcohols, there is obtained a series of the higher homologues of cocaïne. These derivatives possess almost the same physiological properties as cocaïne; at the same time in their therapeutic action they possess no particular advantage over the natural alkaloid. The ethyl derivative, *coca-ethyline*, first prepared by Merck, forms prisms melting at 109°. This may be identical with a coca alkaloid isolated by Günther, which melts at 110–111° and which he regarded as an isomer.

2. CINNAMYLCOCAÏNE.

This base is found in almost all the varieties of coca, but particularly in that from Java, in which it constitutes nearly one half of the entire quantity of the alkaloids. It was discovered by Giesel [13] in 1889. Its constitution was studied by Liebermann,[14] who succeeded in synthesizing it by the action of cinnamic aldehyde on ecgonine and subsequent treatment with methyl alcohol.

Cinnamylcocaïne is accordingly a cocaïne in which the radical of benzoic acid is replaced by that of cinnamic acid.

Cinnamylcocaïne may also be obtained in a crystalline condition by cooling its hot benzol-ligroin solution. It forms needles which melt at 121°. It is almost insoluble in water and ether; easily soluble in alcohol. Its solutions are lævorotatory.

[12] Einhorn, B. 21, 47, 3335; B. 22, Ref. 619; B. 27, 2960, Ref. 953. Einhorn and Willstätter, B. 27, 1523.

[13] Giesel, *Pharmaceutische Zeitung*, 34, 516.

[14] Liebermann, B. 21, 3372.

3 and 4. α- AND β-TRUXILLINE.

In 1887 Hesse[15] isolated from a coca of Truxillo (Peru) an amorphous alkaloid, which he named *cocamine* and to which he assigned the formula $C_{19}H_{23}NO_4$. The following year Liebermann[16] showed that the so-called cocamine was a mixture of two isomeric cocaïnes corresponding to the double formula $C_{38}H_{46}N_2O_8$. On saponifying these alkaloids with barium hydroxide he obtained as decomposition-products ecgonine, methyl alcohol, and two acids of the formula $C_{18}H_{16}O_4$. These last he named α- and *β-truxillic* acid and the corresponding alkaloids, α- and *β-truxilline:*

$$\underset{\text{Truxilline}}{C_{38}H_{46}N_2O_8} + 4H_2O \rightarrow \underset{\text{Truxillic acid}}{C_{18}H_{16}O_4} + \underset{\text{Ecgonine}}{2C_9H_{15}NO_3} + \underset{\text{Methyl alcohol}}{2CH_4O}.$$

Shortly afterwards Liebermann and Drory[17] succeeded in synthesizing the two truxillines by treating ecgonine with the anhydrides of the truxillic acids and methyl alcohol. The constitution of these bases is accordingly analogous to that of the other cocaïnes; they are methyl esters of two *truxillylecgonines*, $(C_9H_{13}NO_3)_2(CH_3)_2C_{18}H_{14}O_2$.

α-Truxilline is amorphous and melts at 80°; it is lævorotatory; it is little soluble in water and ligroin, but readily soluble in other solvents. In taste it is quite bitter.

β-Truxilline possesses similar properties; it is likewise amorphous and begins to melt at 45°; it differs from its isomer in its slight solubility in alcohol.

The Truxlilic Acids.—The constitution of these acids has been made clear through the investigations of Liebermann and his students.[18]

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[15] Hesse, *Pharmaceutische Zeitung*, 32, 407, 668; B. 22, 665; A. 271, 180; J. pr. [2] 66, 401.

[16] Liebermann, B. 21, 2342; 22, 672.

[17] Liebermann and Drory, B. 22, 130, 680.

[18] Liebermann, B. 21, 2342; 22, 124, 130, 680, 782, 2240, 2256, 2261; 23, 317, 2516; 24, 2589; 25, 90; 26, 834; 27, 1410, 1416; 31, 2095.

The truxillic acids, $(C_9H_8O_2)_2$, are polymers of cinnamic acid; on distillation they are converted into this acid. Since they do not absorb bromine and on oxidation with potassium permanganate do not yield benzaldehyde, they apparently have no double bond in the molecule. They are accordingly without doubt derivatives of tetramethylene and probably possess the following constitution:

$$\begin{array}{ccccc} & C_6H_5—CH—CH—COOH \\ & \quad\;\;\; | \quad\;\;\;\; | \\ COOH—CH—CH—C_6H_5 \\ \text{I} \end{array} \qquad \begin{array}{c} C_6H_5—CH—CH—COOH \\ \quad\;\;\; | \quad\;\;\;\; | \\ C_6H_5—CH—CH—COOH \\ \text{II} \end{array}$$

α-Truxillic acid crystallizes from alcohol in needles melting at 274°. It is little soluble in hot water and in all organic solvents. Fusion with caustic potash oxidizes it to benzoic and acetic acids. With phosphorus pentachloride it yields a chloride. When this is heated with sodium α-truxillate there is formed an anhydride of the formula $(C_9H_7O)_2O$. Fuming sulphuric acid converts α-truxillic acid into *truxone*, $(C_9H_6O)_n$, a body which melts at 289° and sublimes without decomposition.

Hausmann[19] obtained truxone in an entirely different way by starting with α-hydrindone:

$$\begin{array}{c} OC—CH_2 \\ |\quad\;\; | \\ H_4C_6—CH_2 \\ \text{α-Hydrindone} \end{array} \qquad \begin{array}{c} OC—CH—CH—CO \\ |\qquad | \qquad | \qquad | \\ H_4C_6—CH—CH—C_6H_4 \\ \text{Truxone} \end{array}$$

This method of synthesis readily explains the formation of a tetramethylene ring in truxone.

The constitution of α-truxillic acid is probably expressed by formula I.

β-Truxillic acid is more soluble in hot water than its isomer. It melts at 206°. On oxidation with potassium permanganate,

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[19] Hausmann, B. 22, 2023.

benzoic acid, and benzil $\begin{array}{l} C_6H_5—CO \\ \quad\;\; | \\ C_6H_5—CO \end{array}$ are formed; the acid consequently contains the complex $\begin{array}{l} C_6H_5—C \\ \quad\;\; | \\ C_6N_5—C \end{array}$

It is depolymerized by heat, being converted into cinnamic acid. By the action of acetic anhydride there is formed an anhydride, $C_{18}H_{14}O_8$, which will condense with resorcin to a fluoresceïn. All these data indicate that β-truxillic acid should be represented by formula II.

Both the truxillic acids, also the anhydrides of these acids, are changed by the action of alkalies into stereoisomeric acids (*δ- and ε-truxillic acids*). In fact there are theoretically possible not less than five stereoisomers of formula I and six of formula II

The synthesis of α-truxillic acid was effected by Riiber [20] in 1902. Cinnamylidene malonic acid, $C_6H_5—CH=CH—CH=C(COOH)_2$, by the action of sunlight is polymerized to a dimolecular substance, which on oxidation yields among other products α-truxillic acid:

$$\begin{array}{r} C_6H_5—CH=CH—CH=C(COOH)_2 \\ (COOH)_2C=CH—CH=CH—C_6H_5 \end{array} \longrightarrow$$

Cinnamylidene malonic acid

$$\begin{array}{r} C_6H_5—CH—CH—CH=C(COOH)_2 \\ |\qquad\; | \qquad\qquad\qquad \\ (COOH)_2C=CH—CH—CH—C_6H_5 \end{array} \longrightarrow$$

Diphenyl-tetramethylene-dimethylene-malonic acid

$$\begin{array}{r} C_6H_5—CH—CH—COOH \\ |\qquad\; | \qquad\qquad \\ HOOC—CH—CH—C_6H_5 \end{array}$$

α-Truxillic acid

It was found later that cinnamic acid itself under the prolonged

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[20] Riiber, B. 35, 2411, 2908. Kohler, Am. Chem. Jour. 28, 233.

action of light polymerized directly to α-truxillic acid. In this reaction the isomeric β-truxillic acid is apparently not formed.

5. Benzoylecgonine.

This derivative, which is a product of the partial saponification of cocaïne, is found already formed, although in very small quantity, in coca-leaves.[21] It bears the formula $C_{16}H_{19}NO_4$ or $C_9H_{14}NO_3(COC_6H_5)$. It crystallizes from hot water in prisms containing four molecules of water. The melting-point of the hydrous body is 92°, of the anhydrous 195°.

Benzoylecgonine differs from the other coca alkaloids in its acid properties; it dissolves in alkalies. It is easily soluble in water and alcohol, insoluble in ether.

As we saw above, benzoylecgonine on hydrolysis is decomposed into ecgonine and benzoic acid. Liebermann and Giesel[22] succeeded in reversing this reaction by heating ecgonine with benzoic anhydride and some water. By treating benzoylecgonine with the proper alcohols and hydrogen chloride, there are formed cocaïne and its homologues.

Ecgonine, $C_9H_{15}NO_3$.—Ecgonine results as a saponification-product of all cocaïnes, which must accordingly be regarded as its esters. It crystallizes with one molecule of water in prisms, which after being dried melt at 198–199°; it is lævorotatory and easily soluble in water.

Ecgonine is a body with a threefold function; it reacts at the same time as a tertiary base, as a monatomic alcohol, and as a monobasic acid. Its tertiary basic character is shown by its uniting with a molecule of alkyl halide to form quaternary salts; its ability to form esters—such as benzoylecgonine—with acid anhydrides and chlorides indicates the presence of an alcoholic hydroxyl group; finally its solubility in alkalies giving rise to salts which are not decomposed by carbonic acid and the ease

[21] Skraup, M. 6, 556. Merck, B. 18, 1594.
[22] Liebermann and Giesel, B. 21, 3196.

with which it is converted into esters in the presence of alcohols and mineral acids point to the existence of a carboxyl group.

The formula $C_9H_{15}NO_3$ may accordingly be expressed as follows:

$$\begin{array}{l} HO-C_8H_{13}\equiv N \\ \quad\quad | \\ \quad\quad COOH \end{array}$$

The fact, however, that ecgonine solutions are neutral in their action toward litmus, led Einhorn to believe that in the free ecgonine the acid and basic groups mutually compensate each other; we would thus have a betaïne-like derivative:

$$\begin{array}{l} HO-C_8H_{13}\equiv NH \\ \quad\quad | \quad\quad\quad | \\ \quad\quad CO——O \end{array}$$

As a matter of course, in the formation of salts the betaïne-like ring is broken and we must in such cases return to the first formula.

Ecgonine possesses a methyl group attached to the nitrogen. This is shown first of all by an observation of Merck,[23] who obtained methylamine by boiling ecgonine with baryta-water. It further results from a reaction noted by Einhorn.[24] When ecgonine is moderately oxidized with potassium permanganate it is converted into a derivative, $C_8H_{13}NO_3$, *norecgonine*, whose esters are secondary bases. Norecgonine crystallizes in needles melting at 233°.

Accordingly the formula of ecgonine may be further expressed as

$$\begin{array}{l} HO-C_7H_{10}=N-CH_3 \\ \quad\quad | \\ \quad\quad COOH \end{array} \quad \text{or} \quad \begin{array}{l} HO-C_7H_{10}=N\langle^{H}_{CH_3} \\ \quad\quad | \quad\quad\quad | \\ \quad\quad CO——O \end{array}$$

What is now the constitution of the complex $C_7H_{10}N$?

This problem has been studied for a long time in a series of

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[23] Merck, B. 19, 3002.

[24] Einhorn, B. 21, 3029.

careful investigations, but only found its solution when the structure of tropine was solved.

Ecgonine, indeed, is most closely related to tropine, since it proves to be a carboxylic acid of the latter.

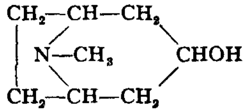
The relation between the two alkaloids appears in a characteristic reaction. Ecgonine may be easily converted into tropidine (page 243):

$$\underset{\text{Ecgonine}}{C_9H_{15}NO_3} \rightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + CO_2 + H_2O.$$

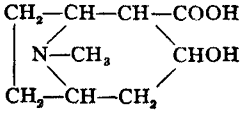
From this all the considerations which have been presented in regard to the constitution of tropine (p. 217) attain new significance.

The oxidation-products of ecgonine and tropine are the same. The action of chromic acid converts both bases into *tropinone*, $C_8H_{13}NO$.[25] If the oxidizing action of the chromic acid is stronger, both yield *tropinic acid*, $C_8H_{13}NO_4$.[26] The acid derived from ecgonine is, however, dextrorotatory, while that from tropine is optically inactive.

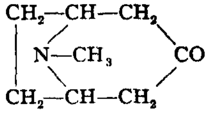
On the basis of the formula developed for tropine, the constitution of ecgonine may be represented as follows:



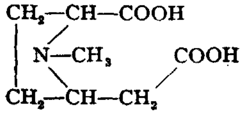
Tropine



Ecgonine



Tropinone



Tropinic acid

In the molecule of ecgonine as in that of tropine there is accordingly present a ring system in which there exist the nucleï of a piperidine, a pyrrolidine, and a cycloheptane ring.

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[25] Willstätter, B. 31, 2655.
[26] Liebermann, B. 23, 2518; 24, 606.

The above oxidation experiments enable us not only to determine the constitution of the atomic-complex $C_7H_{10}NCH_3$ in ecgonine, but they also give us an indication regarding the position of the hydroxyl and carboxyl groups in this complex.

Since both ecgonine and tropine yield the same tropinone and this reaction depends only on the conversion of a CHOH group into a CO group, the OH of the ecgonine molecule must occupy the same position as that of the tropine molecule (page 221).

The position of the carboxyl group is shown from the following consideration. Oxidation converts ecgonine into tropinic acid, and this acid, as we have seen (page 220), is a derivative of *n*-methylpyrrolidine. The carbon atoms of the carboxyl groups consequently did not originally form a part of the pyrrolidine nucleus, but of the piperidine ring.

The presence of a piperidine ring in the ecgonine molecule had indeed been shown much earlier by Stöhr,[27] who obtained *α-ethylpyridine* by distilling ecognine over zinc-dust.

Anhydroecgonine, $C_9H_{13}NO_2$.—Merck[28] observed in 1886 that when ecgonine is heated with phosphorus pentachloride, it loses a molecule of water and is converted into a new base, which he called *anhydroecgonine:*

$$\underset{\text{Ecgonine}}{C_9H_{15}NO_3} \rightarrow \underset{\text{Anhydroecgonine}}{C_9H_{13}NO_2} + H_2O.$$

Einhorn and his students[29] undertook the study of this derivative and made it the subject of a series of investigations which we shall now briefly consider.

Anhydroecgonine is formed from ecgonine not only by the action of phosphorus pentachloride, but also by that of other dehydrating agents, such as sulphuric and hydrochloric acids.

[27] Stöhr, B. 22, 1126.

[28] Merck, B. 19, 3002.

[29] Einhorn, B. 20, 1221; 21, 47, 3029; 22, 399; 23, 1338, 2870; 25, 1394; 26, 324, 451, 2009; 27, 2439, 2823; A. 280, 96.

Anhydroecgonine forms crystals melting at 235°; it is readily soluble in water and alcohol, almost insoluble in ether. Its solutions are lævorotatory. It possesses both a basic and an acid character; like ecgonine it contains a carboxyl group and can be converted into an ester by treatment with alcohol and hydrochloric acid. Its alkali salts are not decomposed by carbonic acid.

On the other hand, anhydroecgonine does not contain the alcoholic group of ecgonine; it is unaffected by acid anhydrides and chlorides. The loss of the alcoholic hydroxyl has given rise to an unsaturated derivative. Anhydroecgonine adds two atoms of hydrogen, of a halogen, a molecule of a halogen hydride, etc. It is accordingly formed by the conversion of the group $—CH_2—CHOH—$ into that of $—CH{=}CH—$, a reaction which is completely analogous to the formation of tropidine from tropine.

When anhydroecgonine is oxidized with potassium permanganate or nitric acid it yields succinic acid; it must accordingly contain also the group $—CH_2—CH_2—$, which is present in this acid.

Heated with hydrochloric acid to 280°, anhydroecgonine is decomposed into carbon dioxide and a base, $C_8H_{13}N$, which is identical with *tropidine* (page 205):[30]

$$\underset{\text{Anhydroecgonine}}{C_9H_{13}NO_2} \rightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + CO_2.$$

This reaction is of the greatest importance, since it shows the close relation that exists between the coca alkaloids and those of the solanaceæ. It suggests the possibility of converting cocaïne into atropine, since the latter base, according to the method of Ladenburg,[31] can be prepared from tropidine.

Anhydroecgonine is apparently then simply a *tropidine monocarboxylic acid.*

For anhydroecgonine there are accordingly possible the following two formulæ:

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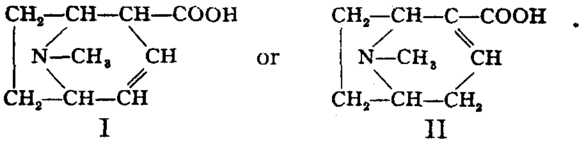
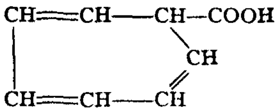
[30] Einhorn, B. 23, 1338.
[31] Ladenburg, B. 12, 941.



Anhydroecgonine

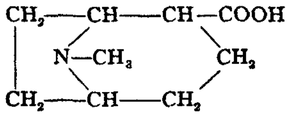
A suggestion of Willstätter[32] leads us to decide in favor of formula I. By the destructive process of Hofmann anhydroecgonine can be converted into a nitrogen-free acid, the so-called *δ-cycloheptatriëne carboxylic acid*, $C_8H_8O_2$:



δ-Cycloheptatriëne carboxylic acid

This acid (melting-point 32°) is changed by the action of alkalies into an isomeric acid, whose double bond is to be regarded as lying next to the carboxyl group.[33] Consequently in the original acid the double bond must be situated between two other carbon atoms, and in anhydroecgonine itself there can be no double bond in the Δ^1 position.

Hydroecgonidine.—When anhydroecgonine is reduced with sodium and amyl alcohol, it absorbs two atoms of hydrogen and is converted into *hydroecgonidine*, $C_9H_{15}NO_2$.[34] The constitution of this derivative follows naturally from that of anhydroecgonine:



Hydroecgonidine

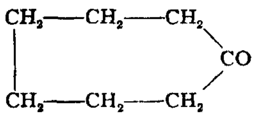
It is a neutral body giving well-defined crystals; it is optically inactive; with mineral acids it forms salts.

[32] Willstätter, B. 31, 2498, 2655.
[33] Buchner, B. 30, 702.
[34] Willstätter, B. 30, 702.

Nitrogen-free Acids which Result from the Decomposition of Ecgonine.—Our present conception of ecgonine and its derivatives as cycloheptane derivatives finds special support in the nitrogen-free acids, which may be obtained from the derivatives of ecgonine by means of Hofmann's process of destructive methylation.

We recall here the conversion already discussed (page 220) of tropinic acid (the oxidation-product of ecgonine and tropine) into *pimelic acid*, $COOH—(CH_2)_5—COOH$.

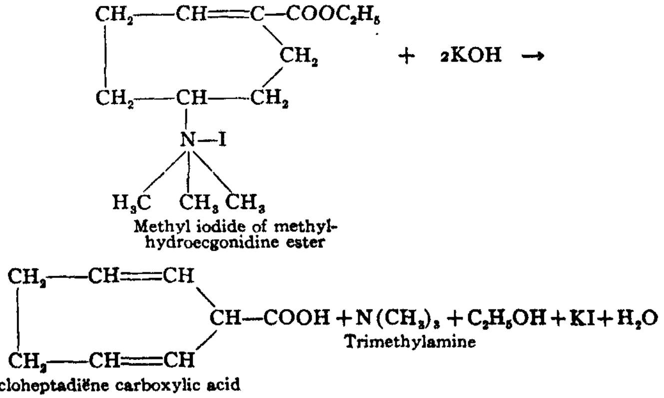
Further, it was found possible to transform hydroecgonidine to *suberone*, $C_7H_{12}O$,



Suberone

in the following way:[35]

By the exhaustive methylation of the ethyl ester of hydroecgonidine (page 244) there is formed the *methyl iodide of methylhydroecgonidine ester*. When this is subjected to the action of caustic alkalies the nitrogen is eliminated and there results an unsaturated nitrogen-free acid, a *cycloheptadiëne carboxylic acid*, $C_8H_{10}O_2$:



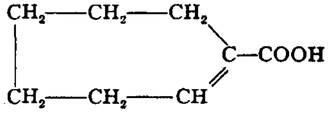
[35] Willstätter, B. 31, 2498.

This cycloheptadiëne carboxylic acid is then reduced to *cycloheptane carboxylic acid*, $C_7H_{13}COOH$, brominated in the α-position, the bromine replaced with hydroxyl by means of baryta-water, and finally the α-oxyacid, $C_7H_{12}(OH)COOH$, thus obtained converted into suberone by oxidation with lead peroxide.

Einhorn[36] in cooperation with Tahara, Friedländer, and Willstätter obtained by the exhaustive methylation of ecgonine and of anhydroecgonine, *p-methylene dihydrobenzoic* acid, $C_8H_8O_2$. This acid may be in part reduced, being converted into *Δ^1-ethyl-cyclopentane carboxylic acid*, $C_8H_{12}O_2$.

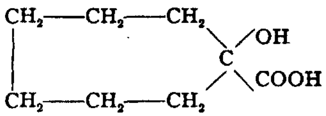
Both these acids are now regarded as cycloheptane derivatives.[37]

Δ^1-Ethylcyclopentane carboxylic acid proved to be identical with *Δ^1-suberene carboxylic acid* (*cycloheptene carboxylic acid*):



Cycloheptene carboxylic acid

The constitution of this acid is shown by the following simple synthesis from *suberone:* The nitrile formed by the addition of prussic acid to suberone yields on saponification ***oxysuberane carboxylic acid:***

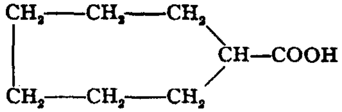


This acid by the elimination of water yields Δ^1-suberene carboxylic acid (cycloheptene carboxylic acid), a crystalline derivative melting at 51–53°.

[36] Einhorn, B. **26**, 324, 1482; **27**. 2823; A. **280**, 96.

[37] Buchner, B. **29**, 106; **30**, 632, 1949; **31**, 2241; **32**, 705. Buchner and Jacobi, B. **31**, 399. Buchner and Lingy, B. **31**, 402, 2247. Buchner and Braren, B. **33**, 684. Willstätter, B. **31**, 1534, 2498; B. **32**, 1635.

On reduction suberene carboxylic acid is converted into the saturated ***suberane carboxylic acid***, $C_8H_{14}O_2$ (*cycloheptane carboxylic acid*):



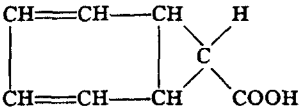
Cycloheptane carboxylic acid

The free acid is an oil; its amide melts at 193–194°.

If now Δ^1-ethylcyclopentane carboxylic acid, $C_8H_{12}O_2$, is identical with cycloheptene carboxylic acid, it follows that *p*-methylene dihydrobenzoic acid, $C_8H_8O_2$, is identical with cycloheptatriëne carboxylic acid (page 244).

This identity was shown by Buchner in another way.

He found that from the action of diazoacetic ester on benzol there is formed the so-called pseudophenylacetic acid, $C_8H_8O_2$:



Pseudophenylacetic acid

This acid by molecular rearrangement yields *isophenylacetic acid*, which occurs in three isomeric forms depending on the position of the double bond. These isophenylacetic acids are true cycloheptatriëne carboxylic acids, which contain three double bonds in a ring of seven carbon atoms. On reduction they yield cycloheptane carboxylic acid (suberane carboxylic acid).

When the cycloheptatriëne carboxylic acids are heated with caustic potash, the position of the double bond is easily shifted and they are converted into their isomeric forms. The most stable of the forms appears to be the one having the double bond next to the carboxyl group (page 244).

We see accordingly that by the exhaustive methylation of anhydroecgonine and of hydroecgonidine there are formed cycloheptatriëne carboxylic acid and cycloheptadiëne carboxylic acid

respectively, and that these acids yield on reduction cycloheptene carboxylic acid and finally cycloheptane carboxylic acid.

The position of the double bonds in the unsaturated acids has not as yet been definitely established.

Dextro-ecgonine.—The formula of ecgonine, as it has been developed above, contains four asymmetric carbon atoms. This makes possible the existence of a large number of stereoisomers of the natural ecgonine. As yet there have been obtained only two of these, of which one is known as dextro-ecgonine. Einhorn and Marquardt[38] prepared this by heating the ordinary lævo-rotatory ecgonine or various natural cocaïnes with an alkali. Dextro-ecgonine differs from its isomer not only in the direction of its rotatory power, but also in its higher melting-point (257°) and in the properties of its salts. Einhorn and his students[39] have carried out the same reactions with dextro-ecgonine as with lævo-ecgonine and have thereby obtained a series of derivatives, of which some are identical with those of the natural base and others differ from these only in their optical properties.

Thus dextro-ecgonine by elimination of water yields an anhydroecgonine, and by oxidation a tropinic acid,[40] both of which are identical with the derivatives obtained from the natural lævo-ecgonine.

This indicates that in the formation of dextro-ecgonine from lævo-ecgonine only the asymmetric carbon atom is concerned which bears the group —HOH.

If dextro-ecgonine is subjected to the action of weaker reagents which leave the HOH group intact, it gives rise to derivatives which differ from those of lævo-ecgonine. Thus potassium permanganate oxidizes dextro-ecgonine to *dextro-norecgonine;* alcohols and hydrochloric acid give rise to dextrorotatory esters; and benzoyl chloride converts the methyl ester into a *dextro-cocaïne.* Dextro-cocaïne is a crystalline derivative melting at

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[38] Einhorn and Marquardt, B. **23**, 468; **24**, Ref. 435.
[39] Einhorn, B. **23**, 468, 979; **24**, 7, Ref. 435; **26**, 962, 1482; **27**, 1880.
[40] Liebermann, B. **24**, 606.

46–47°; in physiological action it closely resembles ordinary cocaïne.

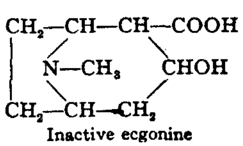
Liebermann and Giesel[41] have also obtained dextro-cocaïne as a side-product in preparing the ester of natural ecgonine. They infer from this that the latter contains some of the dextro-modifitions. Possibly, however, the occurrence of the dextrorotatory alkaloid is to be accounted for by a change of some of the lævo-ecgonine into dextro-ecgonine during the formation of cocaïne and the subsequent conversion of this into the dextrorotatory cocaïne.

Inactive Ecgonine.[42]—Just as ecgonine may be converted into tropine, so from tropine we can derive an inactive ecgonine, which is probably the racemic modification of ordinary ecgonine (*l*-ecgonine).

Tropinone, the oxidation-product of tropine, yields with sodium the derivative $C_8H_{12}NONa$. If this sodium tropinone is now treated with dry carbon dioxide and the addition-product is reduced with sodium amalgam in dilute hydrochloric acid, *inactive ecgonine* is obtained in small quantity.

Inactive ecgonine, $C_9H_{15}NO_3$, separates from alcohol in rhombic crystals, which melt with decomposition at 251°. It is very soluble in water, difficultly so in alcohol. The acid is neutral in reaction.

When the methyl ester of *i*-ecgonine is subjected to exhaustive methylation, it yields the same cycloheptatriëne carboxylic acid as does the ester of ecgonine under like treatment. Its constitution must then be



Inactive ecgonine

From *i*-ecgonine may be synthesized an inactive cocaïne.

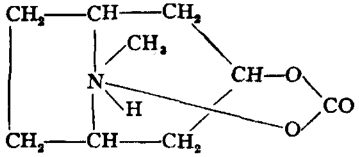
[41] Liebermann and Giesel, B. 23, 508.
[42] Willstätter and Bade, B. 34, 1457. Willstätter, A. 326, 42.

i-Cocaïne is insoluble in water, readily soluble in alcohol and ether. It crystallizes in leaflets which melt at 80°.

It is probable that *i*-cocaïne is the racemic modification of the natural alkaloid, although it has not as yet been separated into its active constituents. This formation of *i*-cocaïne from tropine is of special interest, since it represents the last step in the complete synthesis of the inactive alkaloid.

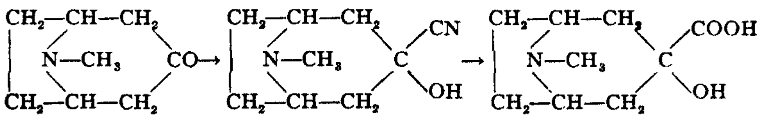
The chief product of the above reaction in which *i*-ecgonine is formed is a substance which is isomeric with the latter derivative and to which we may give the name *pseudoecgonine.*

Pseudoecgonine, $C_9H_{15}NO_3$, crystallizes in monoclinic plates, which melt with decomposition at 201–202°. It dissolves readily in water, but with difficulty in alcohol. In many ways it resembles ecgonine, but, unlike the latter, it cannot be converted into an ester; treatment with hydrogen chloride in alcoholic solution simply decomposes it into carbon dioxide and pseudotropine. Willstätter considers that the constitution of pseudoecgonine is best represented by the formula



Pseudoecgonine

α-Ecgonine.—Another isomer of ecgonine was prepared by Willstätter[43] by treating tropinone with hydrocyanic acid and saponifying the resulting cyanhydrine with hydrochloric acid:



Tropinone — Tropinone cyanhydrin — α-Ecgonine

α-Ecgonine differs from the natural ecgonine in the position

[43] Willstätter, B. 29, 1575, 2216.

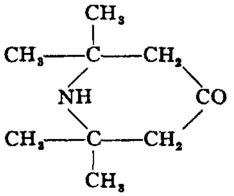
of the carboxyl, which in the new derivative is attached to the same carbon atom as the hydroxyl group.

α-Ecgonine crystallizes from hot water in plates containing ½ or 1 molecule of water; it melts at 305°. It is somewhat soluble in cold water, little soluble in alcohol, and insoluble in ether.

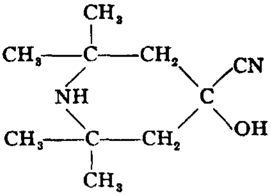
By treating α-ecgonine with methyl alcohol and hydrochloric acid and heating the resulting ester with benzoic anhydride and water Willstätter obtained *α-cocaïne.* This forms prisms melting at 87–88° and, strange to say, is devoid of anesthetic properties.

Eucaïne.—While the transformation of tropine into α-cocaïne did not lead to a derivative possessing the properties of an anesthetic, better results in this direction have been obtained by Merling. This investigator started with ***triacetone amine,*** which in constitution is similar to tropinone and which also can be used advantageously in preparing artificial ***tropeïnes*** (page 227).

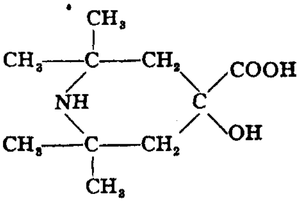
Merling[44] converted triacetone amine into its cyanhydrin and then saponified the latter:



Triacetone amine



Triacetone amine cyanhydrin

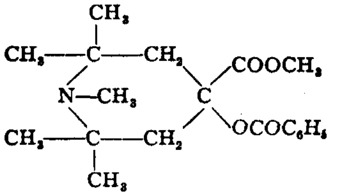


Triacetone alcamine carboxylic acid

The triacetone alcamine carboxylic acid thus formed may now like ecgonine be converted into a cocaïne, or cocaïne-like body,

[44] Merling, *Berichte der deutschen Pharmaceutischen Gesellschaft,* 6, 173.

n-methyl-benzoyltriacetone alcamine carboxylic acid methyl ester (eucaïne):



Eucaïne

Eucaïne crystallizes in shining prisms which melt at 104°; it is employed as an artificial substitute for cocaïne.

6. Tropa-cocaïne (Benzoylpseudotropeïne).

This alkaloid was discovered in 1891 by Giesel [45] in a coca-plant cultivated in Java, and was studied by Liebermann.[46] Its formula is $C_{15}H_{19}NO_2$. It melts at 49° and crystallizes from ether in plates which are insoluble in water, but easily soluble in alcohol and ether. It is optically inactive.

When heated with hydrochloric acid it is decomposed into benzoic acid and a base, $C_8H_{15}NO$; at first Liebermann believed that this base was identical with the *pseudotropine* of Ladenburg which is obtained by the saponification of hyoscine. It was soon shown, however, that the two alkaloids are different. Nevertheless the name originally given is still applied to both alkaloids.

Tropa-cocaïne resembles the tropa alkaloids in that it is decomposed by saponification only into an alcamine and an acid and not into an alcamine, an acid, and an alcohol as is the case with the coca alkaloids proper.

Pseudotropine.—Pseudotropine from tropa-cocaïne crystallizes from a benzol or chloroform solution in prisms which melt at 108°; it boils at 240–241°; it is readily soluble n water,

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[45] Giesel, *Pharmaceutische Zeitung*, 1891, 419.
[46] Liebermann, B. **24**, 2336, 2587; **25**, 927.

alcohol, and ether. Toward litmus it is alkaline in reaction, and optically it is inactive.

The first investigations of Liebermann showed that pseudotropine in its constitution is closely related to tropine. By the dehydrating action of alkalies or acids it yields tropidine; oxidation with chromic acid converts it into tropinic acid. Indeed, the investigations of Willstätter [47] have shown that tropine and pseudotropine are stereoisomers.

If tropinone, the oxidation-product of tropine, is reduced with sodium amalgam, or, better, with sodium and alcohol or moist ether, it is not converted again into tropine, but pseudotropine. There has accordingly occurred a rearrangement of one stereoisomer into the other. The same rearrangement is brought about when tropine is heated with sodium amylate. Further, when pseudotropine is oxidized with chromic acid it is converted into the same *tropinone* that is obtained by the oxidation of tropine. It follows, consequently, that the hydroxyl in pseudotropine is attached to the same carbon atom as it is in tropine.

When pseudotropine is oxidized with potassium permanganate the methyl group attached to the nitrogen is eliminated and there is formed a secondary base, *pseudotropigenine*, $C_7H_{12}NO$. This crystallizes in deliquescent needles, easily soluble in water and alcohol, but little soluble in ether. This derivative is stereoisomeric with the tropigenine derived from tropine (page 205). Both pseudotropigenine and tropigenine on oxidation yield *nortropine*, and this on reduction is converted into pseudotropigenine.

Like tropine, pseudotropine forms esters (*pseudotropeïnes*). These are obtained by heating the base with acid anhydrides or with the acids themselves in the presence of hydrochloric acid. Liebermann [48] prepared some of these derivatives. That which was formed by the action of benzoic anhydride proved to be

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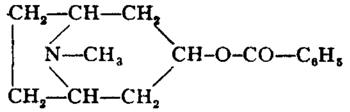
[47] Willstätter, B. 29, 936, 1636, 2231; 31, 1534.

[48] Liebermann, B. 22, 675; 24, 407; 26, 851; 28, 578; 29, 2050; 30, 1113.

identical with benzoyl-pseudotropeïne, or the natural tropa-cocaïne. The following formula must accordingly be assigned to this alkaloid:



Tropa-cocaïne

The *pseudo*tropeïnes of mandelic and tropic acids, unlike the corresponding *tropeïnes*, possess no mydriatic properties. This fact is particularly noteworthy since the artificial atropa alkaloids derived from vinyl diacetone amine also exhibit physiological activity in only one stereoisomeric form (page 229).

Tropylpseudotropeïne forms crystals which melt at 86–88°. It does not appear to be identical with the hyoscine of Ladenburg.

From the above facts we see that tropine may be converted into tropa-cocaïne, i.e., it is possible to pass from a natural solanum base to a coca alkaloid. This affords an interesting demonstration of the close relation between cocaïne and atropine.

7. Hygrine.

Hygrine, $C_8H_{15}NO$, was isolated by Liebermann in 1889 as an alkaloid accompanying cocaïne. It is found particularly in the Peruvian Cusco-leaves, of which it forms about 0.2% According to its composition, hygrine is isomeric with tropine. It is noteworthy that, according to the earlier views, hygrine was supposed to differ from the other solanum and coca alkaloids in that it was a pyrrolidine derivative, while up to that time a pyrrol ring had not been found in any of those alkaloids. Now, however, when all the coca alkaloids are known to be pyrrolidine derivatives, we see that hygrine was the first coca alkaloid whose constitution was correctly indicated.

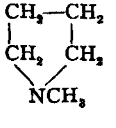
Hygrine is a liquid boiling at 193–195° and possessing a

specific gravity of 0.935 at 17°; optically it is lævorotatory. It is a tertiary base which contains a *n*-methyl, but no methoxyl group. Its oxygen is ketonic in character, since the alkaloid forms an oxime.

On oxidation with chromic acid hygrine yields a monobasic acid, $C_5H_{10}N \cdot COOH$, *hygric acid.* This crystallizes with one molecule of water; the anhydrous acid melts at 164°. It reacts weakly acid, and forms salts with the mineral acids. It is readily soluble in water and alcohol, insoluble in ether.

When hygric acid is heated with sulphuric acid or gold chloride it is decomposed into carbon dioxide and a volatile base resembling piperidine in odor. Liebermann regarded this base, of which he obtained but small quantities, as piperidine, and hygric acid accordingly as a piperidine carboxylic acid. Later Ladenburg obtained all three of the piperidine carboxylic acids theoretically possible by reduction of the corresponding pyridine carboxylic acids (page 55). None of these, however, was identical with hygric acid, consequently Libermann took up anew the study of the latter acid.

He determined first of all by means of the process of Herzig and Meyer that the acid contained a *n*-methyl group; hygric acid accordingly could not be a piperidine derivative. He found further that dry distillation easily decomposed the acid into carbon dioxide and a tertiary base of the formula $C_5H_{11}N$ (boiling-point 81–83°). This base proved to be *n*-methylpyrrolidine:



which had been obtained by Ciamician[49] by the reduction of *n*-methylpyrrol. The identity of the two bases has again been confirmed by the work of Ciamician and Piccinini.[50]

Hygric acid is accordingly a *n-methylpyrrolidine carboxylic*

[49] Ciamician, B. 18, 2079.
[50] Ciamician and Piccinini, B. 30, 1789.

acid, whose carboxyl group, judging from its easy removal, stands in the α-position.

This constitution of hygric acid is confirmed by the synthesis of the acid from methylamine and $\alpha\delta$-dibrompropylmalonic ester, $CH_2Br—CH_2—CH_2—CBr(COOC_2H_5)_2$.[51]

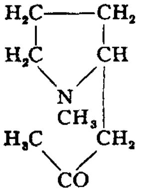
Hygrine now differs from hygric acid by having the C_3H_5O group in place of the carboxyl.

According to the investigations of Liebermann we may then assign to hygrine one of the two following formulæ:

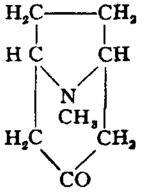
$$\underset{\text{I}}{CH_3N—C_4H_7—CO—CH_2—CH_3} \quad \text{or} \quad \underset{\text{II}}{CH_3N—C_4H_7—CH_2—CO—CH_3}$$

Hygrine

Possibly the preference should be given to the latter, since it more clearly expresses a relation between hygrine and tropine or tropinone:



Hygrine



Tropinone

8. CUSCOHYGRINE.

This alkaloid, $C_{13}H_{24}N_2O$, always accompanies hygrine in the Cusco-leaves, and it was discovered by Liebermann at the same time as the latter. It forms a well-crystallized nitrate by means of which it can be separated from hygrine.

Cuscohygrine is an oil, which can only be distilled without

[51] Willstätter, B. 33, 1160; 35, 620; A. 326, 91.

decomposition *in vacuo*. At 32 mm. it boils at 185°. It is easily soluble in water and forms a crystalline hydrate, $C_{13}H_{24}N_2O + 3\frac{1}{2}H_2O$, which melts at 40–41°; it is optically inactive.

Cuscohygrine is a diacid, bitertiary base; a methyl group is attached to each of its nitrogen atoms. Its constitution is doubtless quite similar to that of hygrine, since oxidation converts it also into hygric acid.

CHAPTER XXIII.

THE ALKALOIDS OF THE POMEGRANATE-TREE.

THE bark of the pomegranate-tree (*Punica granatum* L., family of the Myrtaceæ) contains several alkaloids, which give to the bark its characteristic anthelminthic properties.

Tanret[1] discovered these alkaloids in 1877 and succeeded in isolating the following four:

Pelletierine,	$C_8H_{15}NO$;
Isopelletierine,	$C_8H_{15}NO$;
Methylpelletierine,	$C_9H_{17}NO$;
Pseudopelletierine,	$C_9H_{15}NO$.

These alkaloids receive their names from that of the French chemist Pelletier.

1. PELLETIERINE.

Pelletierine is a colorless oil which soon becomes colored in the air; its specific gravity at 0° is 0.988; it is somewhat soluble in water, easily soluble in alcohol and ether, very soluble in chloroform. Its boiling-point is 195°. It is a strong base, optically dextrorotatory; its sulphate, however, is lævorotatory. When the base is heated with an alkali to 100° it becomes inactive.

2. ISOPELLETIERINE.

Isopelletierine closely resembles the preceding base, of which it is probably a stereoisomer; it is without action on polarized light.

[1] Tanret, C. r. **86**, 1270; **87**, 358; **88**, 716; **90**, 695.

3. METHYLPELLETIERINE.

This is a liquid which boils at 215°; it is somewhat soluble in water, easily soluble in alcohol, ether, and chloroform; its hydrochloride is dextrorotatory.

A possible isomer of methylpelletierine has been isolated by Piccinini [2] from the roots of the pomegranate-tree. It possesses the same composition as this alkaloid, is a tertiary base, and behaves as a ketone.

4. PSEUDOPELLETIERINE.

Of all the alkaloids of the pomegranate-tree pseudopelletierine, called also *methylgranatonine*, is the only one that has been carefully studied.

Ciamician and Silber [3] and later Piccinini [4] carried out a series of investigations with reference to this alkaloid, all of which show that it stands in a close and simple relation to the tropa alkaloids.

Pseudopelletierine crystallizes from ligroin in prisms which melt at 48°; it boils at 246°. It dissolves readily in water, alcohol, ether, and chloroform, more difficultly in ligroin. It is a rather strong base, optically inactive.[5]

The alkaloid contains neither a hydroxyl nor a methoxyl group; its oxygen atom is ketonic in character, since it yields an oxime with hydroxylamine; in general its properties closely resemble those of tropinone.

It possess a methyl group attached to the nitrogen.[6]

Treated with sodium and alcohol, pseudopelletierine adds

[2] Piccinini, *Atti R. Accad. dei Lincei Roma* [5] 8, II, 176.

[3] Ciamician and Silber, B. 25, 1601; 26, 156, 2738; 27, 2850; 29, 481, 490, 2970.

[4] Piccinini, *Atti R. Accad. dei Lincei Roma* [5] 8, I, 392; G. 29, II, 104, 115; 32, I, 260. Piccinini and Cortesse, G. 31, I, 561.

[5] Piccinini, *Atti R. Accad. dei Lincei Roma* [5] 8, II, 219.

[6] Herzig and Meyer, M. 15, 613.

two atoms of hydrogen; the group CO is converted into the group CHOH and there results an alcamine, $C_8H_{13}(OH)=N—CH_3$, which Ciamician and Silber called *methylgranatoline*. This forms crystals which melt at 100° and are soluble in water, alcohol, and ether; it boils at 251°. With acids it yields esters.

When methylgranatoline is oxidized with chromic acid it is first reconverted into pseudopelletierine and then it yields a dibasic acid, *methylgranatic acid*, $C_9H_{15}NO_4$ (prisms melting with decomposition at 240–245°).

If methylgranatoline is treated in the cold with an alkaline permanganate solution, the *n*-methyl group is eliminated and there results a secondary base, *granatoline*, $C_8H_{15}NO$ or $C_8H_{13}(OH)=NH$. This crystallizes from ether in needles melting at 134°. Its hydrochloride distilled with zinc-dust yields pyridine.

By the elimination of a molecule of water, methylgranatoline, $C_9H_{17}NO$, is converted into a new base, *methylgranatenine*, $C_9H_{15}N$ or $C_8H_{12}=N—CH_3$ (boiling-point 186°). This elimination of water is effected indirectly by heating methylgranatoline with hydriodic acid and phosphorus, the hydroxyl group being replaced by iodine; the iodide, $C_9H_{16}IN.HI$, thus formed is then treated with caustic potash, whereby hydriodic acid is split off and methylgranatenine formed.

If methylgranatenine is heated strongly (240°) with hydriodic acid and phosphorus, it is reduced to the saturated derivatives, *methylgranatanine*, $C_8H_{14}=N—CH_3$ (melting-point 49–50°, boiling-point 192–193°), and *granatanine*, $C_8H_{14}=NH$. The latter is a strong base which readily absorbs carbon dioxide from the air. On this account its melting-point (50–60°) has not been sharply determined. By electrolytic reduction methylgranatonine is converted directly into methylgranatanine.

In determining the constitution of pseudopelletierine, the distillation of granatanine hydrochloride over zinc-dust has proved to be of importance; there is thus formed conyrine (α-propylpyridine). This result indicates that pseudopelletierine and its derivatives contain a reduced pyridine ring, from which

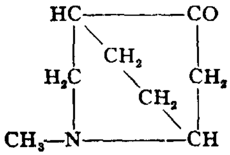
in the α-position there branches a side-chain of at least three carbon atoms.

When the methyl iodide of pseudopelletierine is heated with barium hydroxide it is decomposed into dimethylamine and *granatone*, $C_8H_{10}O$ (a liquid boiling at 197–198°). Oxidation with potassium permanganate converts the latter body into *phenylglyoxylic acid*, $C_6H_5—CO—COOH$.

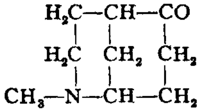
From this it is probable that granatone is a *dihydro-acetophenone*, $C_6H_7—CO—CH_3$.

Thus far the investigation of pseudopelletierine had been carried in 1896 by the labors of Ciamician and Silber. From their work the alkaloid in all its reactions and decomposition-products closely resembled tropinone.

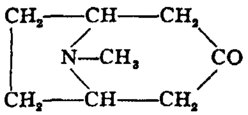
The constitution at that time assigned to tropinone was (page 218)


Tropinone

and so it came about that Ciamician and Silber represented pseudopelletierine by the formula

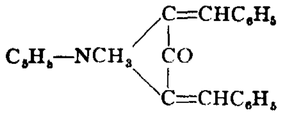

Pseudopelletierine

Shortly, however, after the statement of the above constitution, which appeared to satisfy all the facts observed at that time, the tropinone formula received a modification which was not without influence on that of pseudopelletierine. We have already discussed the considerations which led to an alteration of the above formula for tropinone, and have seen that the constitution of this base is best expressed by the following formula:

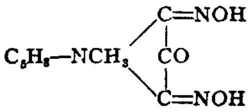


Tropinone

Piccinini now extended the investigations of Ciamician and Silber, following closely the reactions which had led to a modification of the formula for tropinone. He thus found that in pseudopelleticrine the ketone group lies between two CH_2 groups, since condensation of the base with benzaldehyde gives rise to *dibenzylidene methylgranatonine,*



further, with amyl nitrite in a solution of hydrochloric acid there is formed *diisonitroso-methylgranatonine:*



Tropinone and tropinic acid may be made to yield pimelic acid (page 219), so pseudopelletierine (methylgranatonine) may be converted into *suberic acid,* $COOH(CH_2)_6COOH$. From this it follows that pseudopelletierine contains an unbranched chain of *eight* carbon atoms.

The conversion of the alkaloid into the acid is effected in the following way:

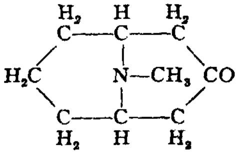
First pseudopelletierine on oxidation forms *methylgranatic acid,* $C_9H_{15}NO_4$. By exhaustive methylation the ester of this acid is converted into *homopiperylene dicarboxylic acid,* $C_8H_{10}O_4$,

$$HOOC—CH{=}CH—CH_2—CH_2—CH{=}CH—COOH,$$

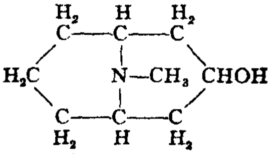
Homopiperylene dicarboxylic acid

which on reduction yields suberic acid.

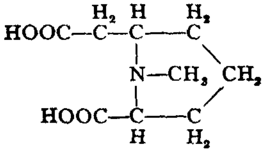
The conversion of pseudopelletierine into suberic acid is thus completely analogous to that of tropinone into pimelic acid. Consequently just as tropinone is to be regarded as a derivative of cycloheptane, so pseudopelletierine is to be considered as a derivative of cyclooctane. The alkaloid may then be regarded as formed by the union of two piperidine rings, whose periphery presents an octane ring. These considerations lead to the following formulæ:



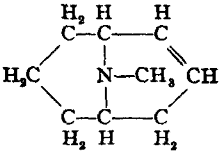
Pseudopelletierine (Methylgranatonine)



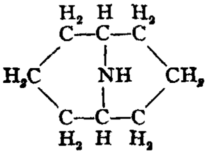
Methylgranatoline



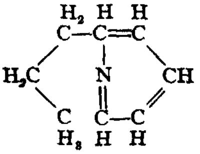
Methylgranatic acid



Methylgranatenine



Granatanine



α-Propylpyridine

The following comparison of the derivatives of tropinone and of pseudopelletierine is instructive:

Pseudopelletierine......... (Methylgranatonine)	$C_9H_{15}NO$	Tropinone...............	$C_8H_{13}NO$
Methylgranatoline.........	$C_9H_{17}NO$	Tropine..................	$C_8H_{15}NO$
Methylgranatenine	$C_9H_{15}N$	Tropidine...............	$C_8H_{13}N$
Methylgranatanine........	$C_9H_{17}N$	Hydrotropidine...........	$C_8H_{15}N$
Methylgranatic acid.......	$C_9H_{15}NO_4$	Tropinic acid............	$C_8H_{13}NO_4$
Granatoline..............	$C_8H_{15}NO$	Tropigenine..............	$C_7H_{13}NO$
Granatanine..............	$C_8H_{15}N$	Norhydrotropidine........	$C_7H_{13}N$
Propylpyridine...........	$C_8H_{11}N$	Ethylpyridine............	C_7H_9N

CHAPTER XXIV.

THE OPIUM ALKALOIDS.

OPIUM is the product resulting from the evaporation of the milky sap that is obtained from certain kinds of poppy-heads, particularly those of *Papaver somniferum* L. (family of the Papaveraceæ). This sap contains a great variety of compounds, such as caoutchouc, fats, resins, gums, sugars, pectines, albuminous substances, mineral salts, certain organic acids (lactic acid, acetic acid, meconic acid), some neutral derivatives of these acids (meconine, meconoïosine, opionine), and a large number of alkaloids.

These last may be separated according to their properties into two distinct groups.

I. The morphine group. Strong bases, very poisonous and containing an oxazine ring:

1. Morphine........	$C_{17}H_{19}NO_3$	$=C_{17}H_{17}NO(OH)_2$
2. Codeïne..........	$C_{18}H_{21}NO_3$	$=C_{17}H_{17}NO(OH)(OCH_3)$
3. Pseudomorphine..	$(C_{17}H_{18}NO_3)_2$	$=[C_{17}H_{16}NO(OH)_2]_2$
4. Thebaïne........	$C_{19}H_{21}NO_3$	$=C_{17}H_{15}NO(OCH_3)_2$

II. The papaverine group. Alkaloids which possess little physiological action and which, as far as their constitution is known, are derivatives of isoquinoline:

5. Papaverine.......	$C_{20}H_{21}NO_4$	$=C_{16}H_9N(OCH_3)_4$
6. Codamine........	$C_{20}H_{25}NO_4$	$=C_{18}H_{18}NO(OH)(OCH_3)_4$
7. Laudanine	"	$=C_{17}H_{15}N(OH)(OCH_3)_3$
8. Laudanidine.....	"	= "
9. Laudanosine.....	$C_{21}H_{27}NO_4$	$=C_{17}H_{15}N(OCH_3)_4$

10. Tritopine.	$(C_{21}H_{27}NO_3)_2O$	=	———
11. Meconidine.	$C_{21}H_{23}NO_4$	=	———
12. Lanthopine.	$C_{23}H_{25}NO_4$	=	———
13. Protopine.	$C_{20}H_{19}NO_5$	=	———
14. Cryptopine.	$C_{21}H_{23}NO_5$	=	$C_{19}H_{17}NO_3(OCH_3)_2$
15. Papaveramine....	$C_{21}H_{21}NO_5$	=	———
16. Narcotine.	$C_{22}H_{23}NO_7$	=	$C_{19}H_{14}NO_4(OCH_3)_3$
17. Gnoscopine.	"	=	"
18. Oxynarcotine.	$C_{22}H_{23}NO_8$	=	$C_{19}H_{14}NO_5(OCH_3)_3$
19. Narceïne.	$C_{23}H_{27}NO_8$	=	$C_{20}H_{18}NO_5(OCH_3)_3$
20. Hydrocotarnine. ..	$C_{12}H_{15}NO_3$	=	$C_{11}H_{12}NO_2(OCH_3)$
21. Xanthaline.	$C_{37}H_{36}N_2O_9$	=	———

The relative proportion of the leading substances found in opium may be approximately represented as follows:

Morphine.	9%
Narcotine.	5%
Papaverine.	0.8%
Thebaïne.	0.4%
Codeïne.	0.3%
Narceïne.	0.2%
Cryptopine.	0.08%
Pseudomorphine.	0.02%
Laudanine.	0.01%
Lanthopine.	0.006%
Protopine.	0.003%
Codamine.	0.002%
Tritopine.	0.0015%
Laudanosine.	0.0008%
Meconic acid.	4.%
Lactic acid.	1.2%
Meconine.	0.3%

1. MORPHINE.

Morphine, as we have already seen (the Introduction), is the first basic compound which was obtained from the plant kingdom. It was isolated in 1806 by Sertürner;[1] its composition, which was determined by Laurent,[2] corresponds to the formula $C_{17}H_{19}NO_3$.

Of all the opium alkaloids morphine occurs in the largest quantities (as high as 23% in some specimens). It has also been found in some other plants, such as *Argemone mexicana* L. (family of the Papaveraceæ) and in wild American hops (*Humulus lupulus* L., family of the *Urticaceæ*).[3]

Morphine crystallizes from alcohol in prisms which contain a molecule of water. It melts with decomposition at about 247°. It is very little soluble in water, ether, benzol, and chloroform, but somewhat readily soluble in alcohol. Its solutions are lævorotatory and are alkaline in reaction. It is bitter in taste and acts as a strong poison. In small doses, on the contrary, its action is soporific and soothing.

Morphine is a tertiary base. At the same time it is a monatomic phenol; it dissolves in alkalies to form salts which contain one atom of metal and are decomposed by carbonic acid. By the action of alkyl halides in the presence of caustic potash, esters are formed in which a hydrogen atom is replaced by an alkyl radical.

On the other hand, morphine forms diacetyl and dibenzoyl derivatives.[4] Hence we conclude that the alkaloid possesses two hydroxyls, one of which is a phenol, the other an alcohol in character.

The alcoholic hydroxyl is readily replaced by chlorine or bromine on treatment with phosphorus trihalide. Under the

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[1] Sertürner, *Trommsdorff, Journal der Pharmacie*, **13**, 1, 234; **14**, 1, 47; **20**, 99.

[2] Laurent, *Journal de Pharmacie*, [3] **14**, 302.

[3] Ladenburg, B. **19**, 783.

[4] Beckett and Wright, Soc. **27**, 1038; **28**, 23, 315. Hesse, A. **222**, 203. E. Merck, *Jahresbericht*, 1898.

action of tin and hydrochloric acid, the haloid derivative is reduced to *desoxymorphine*, $C_{17}H_{19}NO_2$. When warmed with water, brommorphine is converted into the hydrobromide of *isomorphine*, an isomer of morphine:[5]

$$C_{17}H_{18}NO_2Br + H_2O \rightarrow C_{17}H_{19}NO_3 \cdot HBr.$$

The free base melts at 246–247°; it is much more strongly lævorotatory than morphine. From this reaction there have also been obtained small quantities of a second isomer, *β-isomorphine.*

Morphine is quite readily oxidized; even in the cold it reduces gold and silver salts, as well as iodic acid. In alkaline solution it is oxidized by the oxygen of the air; oxidation is also effected by nitrous acid, potassium permanganate, potassium ferricyanide, an ammoniacal copper solution, or by electrolytic decomposition.

In all these reactions there is formed a non-poisonous substance soluble in alkalies which has been studied by several investigators under the names of *oxymorphine*, *oxydimorphine*, and *dehydromorphine*.[6] Hesse[7] showed that the compound is identical with the *pseudomorphine* found in opium (page 282). Its composition, which for a long time was unsettled, is to be represented according to the investigations of Polstorff as $C_{34}H_{36}N_2O_6$ or $(C_{17}H_{18}NO_3)_2$. Accordingly the action of weak oxidizing agents on morphine takes place as follows:

$$\underset{\text{Morphine}}{2C_{17}H_{19}NO_3} + O \rightarrow \underset{\text{Pseudomorphine}}{(C_{17}H_{18}NO_3)_2} + H_2O.$$

By stronger oxidation with dilute nitric acid morphine yields a dibasic acid of the formula $C_{10}H_9NO_9$.[8] This is converted by fuming nitric acid into picric acid.

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[5] Schryver and Lees, Proc. Soc., **16**, 143; **17**, 54; Soc. **77**, 1024; **79**, 563.

[6] Schützenberger, Bl. [2], **4**, 176. Mayer, B. **4**, 121. Nadler, Bl. [2], **21**, 326. Polstorff, B. **13**, 86, etc.; **19**, 1760.

[7] Hesse, A. **141**, 87; Suppl. **8**, 267.

[8] Chastaing, C. r. **94**, 44.

Fused with caustic potash, morphine, according to Barth and Weidel,[9] gives rise to protocatechuic acid.

When the alkaloid is heated with concentrated hydrochloric acid, methyl chloride is not liberated; consequently morphine does not contain a methoxyl group. A *n*-methyl group, however, was found by Herzig and Meyer.[10]

Acids such as sulphuric, hydrochloric, phosphoric, and oxalic, the alkalies, and zinc chloride have a twofold action on morphine.[11] In one case they effect condensation (*trimorphine*, *tetramorphine*), in another dehydration in accordance with the equation:

$$C_{17}H_{19}NO_3 \rightarrow C_{17}H_{17}NO_2 + H_2O.$$

The product of the latter reaction, *apomorphine*, is an amorphous base, easily oxidized, little soluble in water but soluble in alcohol, ether, and chloroform. In its physiological properties it is quite different from morphine; it no longer acts as a narcotic but as a strong emetic.[12]

The constitution of morphine is discussed under codeïne.

2. CODEÏNE.

Codeïne was isolated from opium in 1892 by Robiquet.[13] It is found in much smaller quantities than morphine (0.2–0.8%). Its formula was determined by Gerhardt [14] in 1843 as $C_{18}H_{21}NO_3$. Codeïne crystallizes either with one molecule of water or in the anhydrous condition and melts at 155°; it is little soluble in water, but readily soluble in alcohol, chloroform, and ether; in alkalies it is almost insoluble. It is a tertiary base; its solutions

[9] Barth and Weidel, M. 4, 700.

[10] Herzig and Meyer, M. 18, 379.

[11] Matthiessen and Wright, A. Suppl. 7, 172, 364. Wright, Soc. 25, 653 Mayer, B. 4, 121. Mayer and Wright, Soc. 26, 215, 1082. Beckett and Wright, Soc. 28, 698.

[12] Danckwortt, A. Pharm. 228, 572.

[13] Robiquet, A. ch. [2], 51, 259; A. 5, 106.

[14] Gerhardt, A. ch. [3], 7, 253.

are alkaline in reaction, bitter in taste, and optically lævorotatory. In physiological behavior codeïne closely resembles morphine; indeed, it stands in close chemical relation to the latter, forming as it does a higher homologue.

Codeïne possesses but one hydroxyl group; on treatment with acetyl chloride there is formed a monacetyl derivative.[15] By the method of Zeisel it can be shown that the molecule contains a methoxyl group.[16]

With halogens, nitric acid, etc., codeïne like aromatic derivatives yields substitution-products;[17] indeed, in its reactions it is not unlike dimethylaniline. Thus with nitroso-dimethylaniline it yields a violet dyestuff, which appears to belong to the class of the indamines;[18] with formaldehyde it gives a condensation-product, *dicodeylmethane*, $CH_2(C_{18}H_{20}NO_3)_2$, with the same ease with which formaldehyde condenses with dimethylaniline to form tetramethyl-diamidodiphenylmethane, $CH_2[C_6H_5N(CH_3)_2]_2$. These reactions seem to indicate that the nitrogen atom in codeïne is directly attached to a benzol nucleus.

With phosphorus tribromide codeïne yields bromcodeïne, $C_{17}H_{17}O(OCH_3)NBr$. When warmed with water, this derivative is converted into the hydrobromide of *isocodeïne*, $C_{17}H_{18}O_2(OCH_3)N \cdot HBr$. This formation of an isomeric codeïne is completely analogous to the conversion of morphine into isomorphine (page 267).

When codeïne is treated with mild oxidizing agents it does not yield a derivative analogous to pseudomorphine. Vongerichten[19] explains this by considering that the formation of pseudomorphine from morphine is conditioned on the free phenol-hydroxyl present in the alkaloid, whereas in codeïne this hydroxyl is alkylated.

Dilute sulphuric acid converts codeïne into an isomer, *pseudocodeïne*, a lævorotatory base which melts at 180°.[20]

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[15] Wright, Soc. 27, 1031.
[16] Herzig and Meyer, M. 15, 613.
[17] Anderson, A. 77, 341.
[18] Cazeneuve, Bl. [3], 5, 857; C. r. 112, 805.
[19] Vongerichten, A. 294, 206.
[20] Merck, A. Pharm. 229, 161. Schmidt and Göhlich, A. Pharm. 231, 235.

On treatment with dehydrating agents (zinc chloride, sulphuric, oxalic, phosphoric acids, etc.) the alkaloid behaves like morphine; it either forms various condensation-products (*dicodeïne, tricodeïne, tetracodeïne*),[21] or by loss of water is converted into *apocodeïne*, $C_{18}H_{19}NO_2$.[22]

The general behavior of codeïne, indeed, most closely resembles that of morphine, and we know to-day that these two alkaloids are quite nearly related to each other, codeïne being the monomethyl ester of morphine; between them obtains the same simple relation that is found between anisol and phenol:

Morphine, $C_{17}H_{17}NO(OH)_2$;
Codeïne, $C_{17}H_{17}NO(OH)(OCH_3)$.

This close relation of the two alkaloids was shown to be probable by the work of Matthiessen and Wright [23] in 1869. These investigators, having subjected codeïne to the action of concentrated hydrochloric acid at a temperature of 100°, obtained a chlor-derivative which they called *chlorcodide:*

$$\underset{\text{Codeïne}}{C_{18}H_{21}NO_3} + HCl \rightarrow \underset{\text{Chlorcodide}}{C_{18}H_{20}ClNO_2} + H_2O.$$

This derivative crystallizes in leaflets melting at 148°. On being heated with hydrochloric acid to 150°, it is decomposed into methyl chloride and *apomorphine:*

$$\underset{\text{Chlorcodide}}{C_{18}H_{20}ClNO_2} \rightarrow \underset{\text{Apomorphine}}{C_{17}H_{17}NO_2} + CH_3Cl.$$

According to the above formulæ we see that the action of the hydrochloric acid is to remove from codeïne a methyl group and a molecule of water. Thus this decomposition of codeïne yields the same product as is derived directly by the dehydration of morphine. Consequently we may assume that morphine and

[21] Wright, Soc. **25**, 506.
[22] Matthiessen and Wright, A. **158**, 131.
[23] Matthiessen and Wright, A. Suppl. **7**, 364.

codeïne differ only in this, that one of the hydroxyls of the former is in the latter replaced by a methoxyl group.

This view was fully confirmed by the ready conversion of morphine into codeïne, which was first effected by Grimaux in 1881. This was brought about by heating morphine with methyl iodide and caustic potash or sodium methylate:

$$\underset{\text{Morphine}}{C_{17}H_{17}NO(OH)_2} + CH_3I + KOH \rightarrow$$

$$\underset{\text{Codeïne}}{C_{17}H_{17}NO(OH)(OCH_3)} + KI + H_2O.$$

The same reaction takes place when an alcoholic morphine solution is heated for two hours with potassium methyl sulphate with the addition of some alkali.[24] The potassium methyl sulphate may be replaced by the neutral dimethyl sulphate.[25] Morphine may also be converted into codeïne by the action of diazomethane:[26]

$$\underset{\text{Morphine}}{C_{17}H_{17}NO(OH)_2} + \underset{\text{Diazomethane}}{CH_2N_2} \rightarrow \underset{\text{Codeïne}}{C_{17}H_{17}NO(OH)(OCH_3)} + N_2.$$

The different methods of preparing codeïne and the almost complete insolubility of the alkaloid in alkalies show that of the two hydroxyl groups of morphine it is the phenol hydroxyl which has been alkylated.

Just as codeïne is obtained from morphine, so we may introduce the ethyl group to form *codethyline*, $C_{17}H_{17}NO(OH)(OC_2H_5)$. This melts at 83° and like codeïne is very poisonous.

As we see from the previous considerations, morphine and codeïne possess the common atomic grouping $C_{17}H_{17}NO$. The study of this complex has engaged the attention of numerous in-

[24] Knoll, D. R. P. 39887 (August 7, 1886).

[25] Merck, D. R. P. 102634 (May 22, 1898).

[26] Bayer, D. R. P. 92789 (July 9, 1896). Baeyer, D. R. P. 95644 (April 13, 1897).

vestigators.[27] We are particularly indebted to Vongerichten[28] and Knorr[29] for the knowledge which we have regarding the molecule of these alkaloids.

The starting-point for investigations in this direction was an important observation made by Vongerichten and Schrötter in 1881. By the distillation of morphine over zinc-dust they obtained as the chief product *phenanthrene;* in the same reaction there are also formed ammonia, trimethylamine, pyrrol, pyridine, a little quinoline (?), and a base of the formula $C_{17}H_{17}N$, which has received the name *morphidine* and which has now been shown to be a mixture of two bases, $C_{16}H_{11}N$ and $C_{10}H_9N$.

According to this observation, morphine appeared to be a derivative of phenanthrene. It was necessary, however, to secure a further confirmation of this result through reactions which take place at a lower temperature, since distillation with zinc-dust is a pyrogenetic process, which not only effects decomposition but which often also leads to unexpected syntheses, thus giving rise to new secondary products.

Vongerichten and Schrötter had recourse to Hofmann's process of exhaustive methylation (page 29). They applied this, however, not to morphine itself, but to its monomethyl derivative, codeïne. On distillation codeïne methyl hydroxide yields, as Grimaux had already shown, a tertiary base, *methylcodeïne,* later called by Hesse *methylmorphimethine:*

$$(OH)(CH_3O)C_{17}H_{17}O{\equiv}N{<}^{CH_3}_{OH} \rightarrow$$

Codeïne methyl hydroxide

$$(OH)(CH_3O)C_{17}H_{16}O{=}N{-}CH_3 + H_2O.$$

Methylmorphimethine

[27] Vongerichten and Schrötter, B. **15**, 1484, 2179; A. **210**, 396. Grimaux, C. r. **93**, 591. Hesse, A. **222**, 203. Fischer and Vongerichten, B. **19**, 792. Skraup and Wiegmann, M. **10**, 101, 732. Pschorr and Sumuleanu, B. **33**, 1810. Pschorr and Jaeckel, **35**, 4377. Pschorr and Seydel, B. **35**, 4400. Vongerichten and Müller, B. **36**, 1590.

[28] Vongerichten, B. **29**, 65; **30**, 2439; **31**, 51, 2924, 3198; **32**, 1521; **33**, 352, 1824; **34**, 767, 1162, 2722; **35**, 4410.

[29] Knorr, B. **22**, 181, 1113; **27**, 1144; **30**, 910, 918; **31**, 1071; **32**, 736, 742; **36**, 3074; A. **301**, 1; **307**, 171. Knorr and Smiles, B. **35**, 3009. Knorr and Hawthorne, B. **35**, 3010. Knorr and Ach, B. **36**, 3067

Methylmorphimethine is a crystalline body which melts at 118.5° and is lævorotatory. It still contains the hydroxyl group of codeïne, since it forms a monacetyl derivative. Physiologically it has no action either as a sedative or a hypnotic.

Methylmorphimethine has now become an essential starting-point for the investigation of morphine and codeïne. When it is heated with hydrochloric acid or acetic anhydride, it is decomposed into two substances, one only of which contains nitrogen:

$$\begin{matrix}OH\\CH_3O\end{matrix}\Big\rangle C_{17}H_{16}O{=}N{-}CH_3 \rightarrow$$

$(C_{19}H_{23}NO_3)$
Methylmorphimethine

$$\begin{matrix}OH\\CH_3O\end{matrix}\Big\rangle C_{14}H_8 + HO{-}C_2H_4{-}N(CH_3)_2$$

$(C_{15}H_{12}O_2)$ Methyldioxy-phenanthrene

$(C_4H_{11}NO)$ Dimethyloxyethylamine

The nitrogen-free decomposition-product was studied carefully by Vongerichten, the other, the basic-product, by Knorr. We shall now discuss these two derivatives in order.

The first, $C_{15}H_{12}O_2$, is a phenol and from its composition and general properties, as also by its resolution into phenanthrene, is shown to be a *monomethyl ether of dioxyphenanthrene.* The free dioxyphenanthrene, $C_{14}H_{10}O_2$, has received the name of *morphol.*

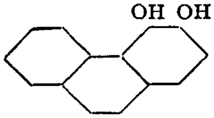
This morphol further shows its relation to phenanthrene by its oxidation with chromic acid to a *dioxyphenanthraquinone* (*morphol quinone*), $C_{14}H_8O_4$ (red flakes).

In this conversion to a quinone, the two hydroxyls of morphol are unaffected. This shows that they are not attached to the adjacent carbon atoms of the phenanthrene nucleus.

It can be shown further that both the hydroxyls are in *one* ring, since oxidation with potassium permanganate converts morphol quinone into phthalic acid:

$$\begin{array}{ccc} \begin{array}{l} C_6H_4 \text{———} CH \\ | \qquad\qquad \| \\ C_6H_2(OH)_2 {-} CH \end{array} & \begin{array}{l} C_6H_4 \text{———} CO \\ | \qquad\qquad | \\ C_6H_2(OH)_2 {-} CO \end{array} & \begin{array}{l} C_6H_4 \text{——} COOH \\ | \\ COOH \end{array} \\ \text{Morphol} & \text{Morphol quinone} & \text{Phthalic acid} \end{array}$$

Morphol is 3,4-*dioxyphenanthrene:*

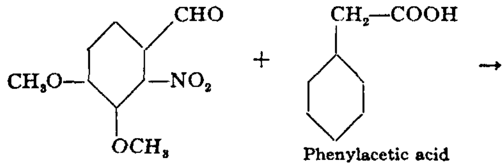


Morphol

The ortho-position of the two hydroxyls with reference to each other is suggested by the formation of protocatechuic acid, when morphine is fused with caustic potash. It is indicated strongly in the behavior of morphol as a dyestuff. Vongerichten called attention to this behavior in an interesting way. Morphol colors mordanted fibres, while its methyl ether is without dyeing properties. In connection with this behavior Vongerichten noted an observation which Liebermann and von Kostanecki [30] had made, that only those oxy-derivatives of anthraquinone color mordanted fibres which have *two* free hydroxyls in an ortho-position, and indeed in a position as near as possible to the chromophoric nucleus (alizarine position).

This strongly presumptive evidence has fortunately been fully confirmed by the direct synthesis of morphol and some of its derivatives.

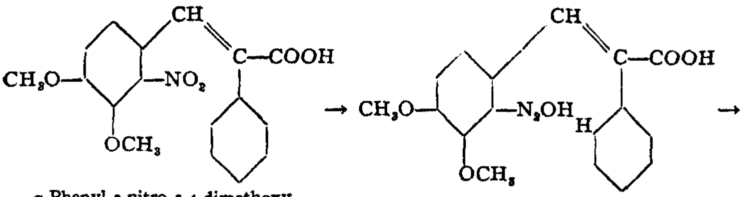
From the condensation of 2-nitrovanillin methyl ether and the sodium salt of phenylacetic acid (Perkin's reaction), Pschorr and Sumuleanu [31] obtained α-phenyl-2-nitro-3,4-dimethoxycinnamic acid. When successively reduced and diazotized, this acid may be converted into 3,4-dimethoxyphenanthrene-9-carboxylic acid, which, on distillation, yields carbon dioxide and 3,4-*dimethoxyphenanthrene:*



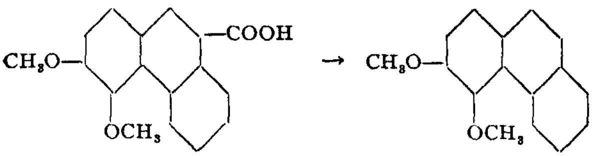
2-Nitrovanillin methyl ether   Phenylacetic acid

[30] Liebermann and von Kostanecki, A. 240, 245. Liebermann, B. 21, 2502; 26, 1575. von Kostanecki, B. 20, 3146.

[31] Pschorr and Sumuleanu, B. 33, 1810.



α-Phenyl-2-nitro-3,4-dimethoxy-cinnamic acid

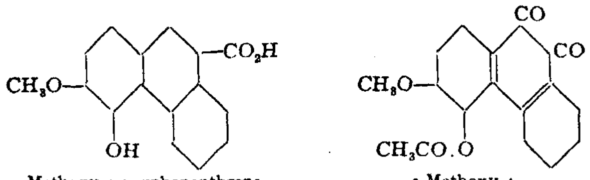


3,4-Dimethoxyphenanthrene-9-carboxylic acid

3,4-Dimethoxyphenanthrene

3,4-Dimethoxyphenanthrene proved to be identical with dimethylmorphol prepared by Vongerichten from methylmorphol, the decomposition-product of codeïne.

The position of the methyl group in methylmorphol remains to be determined. This has recently been effected by Pschorr and Vogtherr [32] through a series of reactions similar to the above. Starting with 2-nitroisovanillin they obtained 3-methoxy-4-oxyphenanthrene-9-carboxylic acid, which oxidation with chromic acid in a solution of glacial acetic acid converted into 3-methoxy-4-acetoxy-phenanthraquinone (melting-point 205–206°).



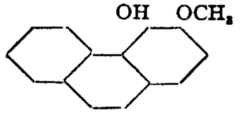
3-Methoxy-4-oxyphenanthrene-9-carboxylic acid

3-Methoxy-4-acetoxyphenanthraquinone

This last derivative is identical with acetyl-methylmorphol quinone, which Vongerichten [33] had earlier prepared from

[32] Pschorr and Vogtherr, B. 35, 4412.
[33] Vongerichten, B. 31, 52.

methylmorphol. Methylmorphol is consequently 3-*methoxy*-4-*oxyphenanthrene:*



Methylmorphol

The isomeric 3-oxy-4-methoxyphenanthrene has been synthesized; it differs in its properties from methylmorphol.

Morphol is not the only nitrogen-free decomposition-product of morphine and codeïne that contains the phenanthrene nucleus. From methylmorphimethine there may be obtained the derivative *morphenol*, $C_{14}H_8O_2$, which differs from morphol by possessing two hydrogen atoms less, but otherwise quite closely resembles the latter derivative; reduction, indeed, converts morphenol into morphol.

To prepare morphenol, methylmorphimethine is heated with acetic anhydride. About one-half the base experiences the decomposition already mentioned (page 273) into oxymethoxyphenanthrene and dimethyloxyethylamine; the remainder, however, is not decomposed, but undergoes a molecular rearrangement, being converted into a stereoisomeric derivative. This new derivative, *β-methylmorphimethine*, is amorphous, dextrorotatory, in its physiological action similar to the original substance, α-methylmorphimethine.

The methyl hydroxide of β-methylmorphimethine on being heated suffers decomposition into trimethylamine and the *methyl ether of morphenol*, from which morphenol itself may be directly prepared.

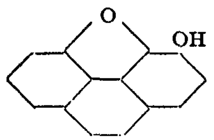
Morphenol crystallizes in needles, melts at 145°, and is readily soluble in alcohol and ether, as also in sodium hydroxide.

The substance interests us in particular, since it is the decomposition-product of morphine and codeïne which on distillation with zinc-dust is readily converted into phenanthrene and thereby indicates that these alkaloids are derivatives of this hydrocarbon. The constitution of morphenol must be quite

similar to that of morphol, since, as we have shown above, it is converted into the latter by reduction:

$$C_{14}H_7O(OH) + 2H \rightarrow C_{14}H_8(OH)_2.$$

We may then extend to morphenol the constitutional formula of morphol. Vongerichten considers that the following formula best expresses the constitution of morphenol:



Morphenol

In addition to the two methylmorphimethines mentioned above, there appear to be two other isomers, γ- and δ-methylmorphimethine.[34] These are obtained from isocodeïne in much the same way that the α- and β-derivatives are formed from codeïne. Isocodeïne in turn is derived from codeïne by treatment of the latter with phosphorus tribromide and subsequent decomposition of the brom-derivative with water.

We now turn to the consideration of the nitrogenous decomposition-product, which is formed by heating methylmorphimethine with acetic anhydride and which has the formula $C_4H_{11}NO$ (page 273).

Of these four carbon atoms two at least must be united to the nitrogen and one of these must be a methyl group. The presence of the methyl group is naturally shown from the derivation of the base. A methyl group was added to methylmorphimethine in its formation from codeïne; furthermore, codeïne itself possesses a *n*-methyl group. This last is shown by the direct determination of the *n*-methyl group in morphine and codeïne by the method of Herzig and Meyer;[35] it follows also from the splitting off of methylamine when morphine is heated

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[34] Schryver and Lees, Soc. 79, 563. Knorr and Hawthorne, B. 35, 3010.

[35] Herzig and Meyer. M. 10, 101.

with a very concentrated solution of caustic potash,[36] and likewise from the elimination of trimethylamine when the methyl hydroxide of methylmorphimethine is heated.

The complete determination of the constitution of the base $C_4H_{11}NO$ was made by Knorr. He found that this base was identical with one already prepared by Ladenburg by the action of chlorhydrin on dimethylamine. This *oxyethyldimethylamine* is a liquid boiling at 128°, and is represented by the formula

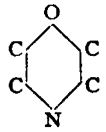
$$\begin{array}{l} CH_2OH \\ | \\ CH_2N(CH_3)_2. \end{array}$$

By the action of methyl iodide the morphine base is converted into the hydriodide of *choline:*

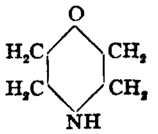
$$\begin{array}{l} CH_2OH \\ | \\ CH_2N(CH_3)_3I. \end{array}$$

This affords additional confirmation of the accepted constitution.

From the formation of oxyethyldimethylamine Knorr concludes that morphine contains an *oxazine* ring:



The basal substance corresponding with this conception,



he calls *morpholine.*

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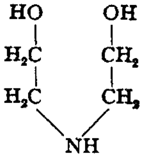
[36] Wertheim, A. 37, 210.

Morpholine is the inner anhydride of *diethanol-amine:*



Diethanol-amine

The latter substance is obtained by adding ethylene oxide to concentrated ammonia, and is converted into morpholine on being heated for eight hours at 160–170° with 70% sulphuric acid.

Morpholine, C_4H_9NO, is an oil which boils at 128–130°; it is strongly basic, and in odor and general behavior closely resembles piperidine.

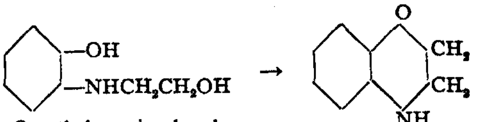
Like morpholine, methylmorpholine, $C_4H_8ON—CH_3$, may be formed by dehydrating *diethanol-methylamine*,

$$OHCH_2—CH_2—NCH_3—CH_2—CH_2OH.$$

Several other methods have been proposed for the synthesis of morpholine and its derivatives.[37]

Morphine and codeïne thus appear to be ring systems containing the phenanthrene complex in connection with a morpholine or morpholine-like ring.

Knorr attempted to synthesize such ring systems in various ways. From oxyethyl-*o*-amidophenol he prepared *phenmorpholine*, a colorless oil boiling at 268°:

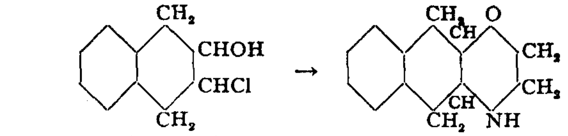


Oxyethyl-*o*-aminophenol

Phenmorpholine

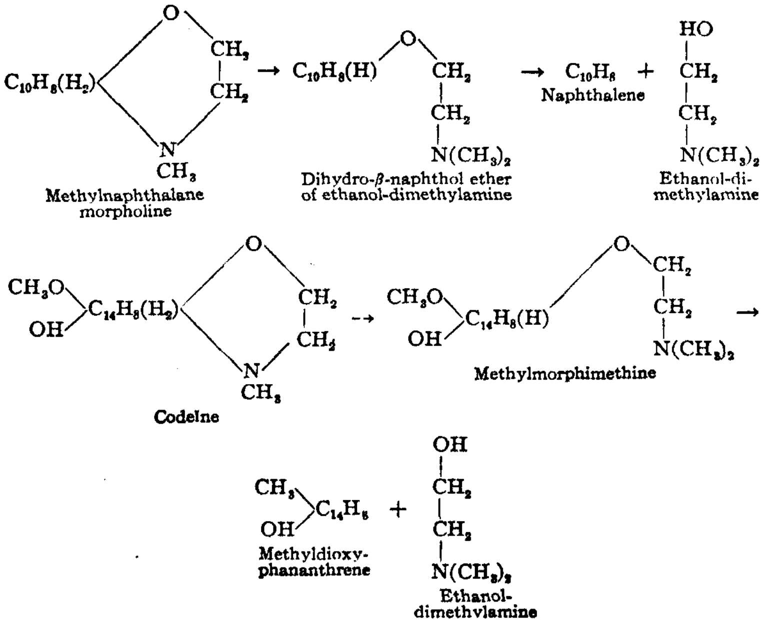
[37] *Central-Blatt*, 1901, I, 978, 1074. Marckwald and Chain, B. 34, 1157. Sand, B. 34, 2906.

By condensation of *tetrahydronaphthalene chlorhydrin* with *ethanol-amine*, $NH_2CH_2CH_2OH$, there was obtained ***naphthalane morpholine***,



Tetrahydronaphthalene chlorhydrin — Naphthalane morpholine

This derivative forms crystals which melt at 62–63°; it boils at 312°. The *n*-alkyl derivatives of naphthalane morpholine in their physiological action closely resemble morphine. *n-Methylnaphthalane **morpholine*** is of particular interest, since its methyl hydroxide when heated is decomposed into naphthalene and ethanol-dimethylamine. In this behavior it is quite like codeïne, whose decomposition into methyldioxyphenanthrene and ethanol-dimethylamine formed the starting-point of these considerations (page 273). The following formulæ make clear these reactions:



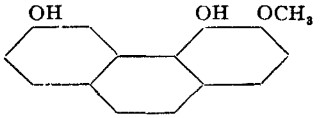
The close relation between codeïne and thebaïne recently shown by Knorr [38] throws some light on the manner in which the ethanol-methylamine complex is attached to the phenanthrene ring in the former of these alkaloids.

Codeïne may be oxidized to a ketone, *codeïnone:*

$$\underset{\text{Codeïne}}{C_{18}H_{21}NO_3} + O \rightarrow \underset{\text{Codeïnone}}{C_{18}H_{19}NO_3} + H_2O.$$

Like thebaïne (page 283) codeïnone when heated with dilute hydrochloric acid yields *thebenine* and with fuming hydrochloric acid forms *morphothebaïne.*

On treatment with acetic anhydride codeïnone is decomposed into ethanol-methylamine and 3-*methoxy*-4,6-*dioxyphenanthrene,*

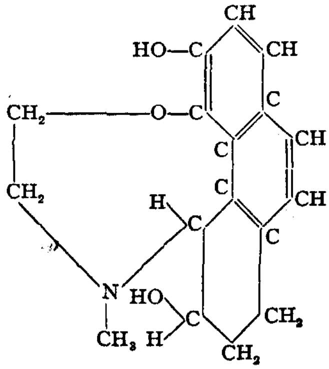


3-Methoxy-4,6-dioxyphenanthrene

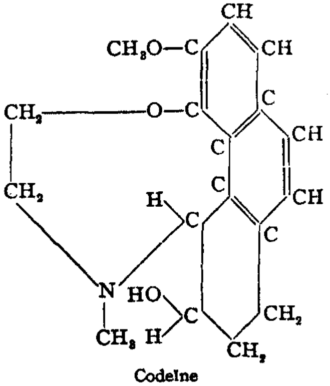
a substance closely related to thebaol (page 285).

Codeïne is accordingly a derivative of 3,4,6-trioxyphenanthrene.

Taking into consideration both the work of Knorr and that of Vongerichten, we may provisionally represent morphine and codeïne by the following formulæ:



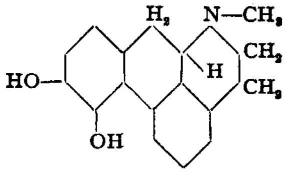
Morphine



Codeïne

[38] Ach and Knorr, B. 36, 3067. Knorr, B. 36, 3074.

According to Pschorr, Jaeckel, and Fecht[39] the constitution of apomorphine (page 268) may possibly be represented by the formula



Apomorphine

This, however, is not in accord with the preceding formulæ for morphine and codeïne.

They have shown that apomorphine may be obtained as a crystalline derivative, that it contains two hydroxyls (dibenzoyl derivative), that the tertiary nitrogen somewhat readily assumes a secondary condition, probably due to the rupture of the nitrogenous ring (triacetyl and tribenzoyl derivatives). On exhaustive methylation the base is decomposed into trimethylamine and a nitrogen-free unsaturated derivative of phenanthrene.

3. PSEUDOMORPHINE.

This alkaloid was obtained from opium by Pelletier and Thiboumery[40] in 1835. Hesse[41] assigned to it at first the formula $C_{17}H_{19}NO_4$ and showed its identity with the derivative which had been prepared by Schützenberger by the moderate oxidation of morphine. Polstorff[42] showed later that the composition of pseudomorphine is $C_{34}H_{36}N_2O_6$, i.e., $(C_{17}H_{18}NO_3)_2$, a correction which was accepted by Hesse.[43]

Pseudomorphine crystallizes in leaflets which on being heated decompose without melting; it is insoluble in water, alcohol, ether, and the alkali carbonates, but soluble in caustic alkalies; it is lævorotatory and non-poisonous. It is a weak base, biter-

[39] Pschorr, Jaeckel, and Fecht, B. **35**, 4377.
[40] Pelletier and Thiboumery, *Journal de Pharmacie*, [2] **21**, 569; A. **16**, 49.
[41] Hesse, A. **141**, 87; Suppl. **8**, 267.
[42] Polstorff, B. **19**, 1760.
[43] Hesse, A. **235**, 229.

tiary in character. Its molecule contains four hydroxyl groups as Danckwortt[44] has shown by the preparation of a tetra-acetyl derivative, $C_{34}H_{32}N_2O_6(C_2H_3O)_4$.

From its mode of formation by the oxidation of morphine, pseudomorphine may be regarded as a product resulting from the condensation of two molecules of morphine with the loss of two atoms of hydrogen:

$$2C_{17}H_{19}NO_3 + O \rightarrow (C_{17}H_{18}NO_3)_2 + H_2O.$$

As yet, however, it has not been found possible to reconvert pseudomorphine into morphine by reduction.

4. THEBAÏNE.

Thebaïne, or *paramorphine*, was discovered by Pelletier and Thiboumery[40] in 1835. In composition it corresponds to the formula $C_{19}H_{21}NO_3$. It crystallizes from alcohol in thin leaflets which melt at 193°; it is lævorotatory, insoluble in water and alkalies, little soluble in ether, but readily soluble in alcohol, chloroform, and benzol; it is a powerful tetanic poison.

Thebaïne is a tertiary base; it contains no hydroxyl group, since it is unaffected by both acetic anhydride and phosphorus pentachloride.[45] On the other hand, Howard[46] has shown that it possesses two methoxyl groups; heated with *concentrated* hydrochloric acid, two molecules of methyl chloride are eliminated and there is obtained the derivative *morphothebaïne*, $C_{17}H_{17}NO_3$,

$$C_{17}H_{15}NO\begin{cases}OH\\OH\end{cases}$$

This was later regarded by Freund[47] as $C_{18}H_{19}NO_3$,

$$C_{17}H_{15}NO\begin{cases}OH\\OCH_3\end{cases}$$

[44] Danckwortt, A. Pharm. 228, 572.
[45] Hesse, A. 153, 47.
[46] Howard, B. 17, 527; 19, 1596.
[47] Freund, B. 32, 168.

Morphothebaïne crystallizes from benzol in plates which melt at 190–191°; it is a tertiary base, weakly poisonous, insoluble in alcohol and ether, little soluble in water, but readily soluble in alkalies.

Dilute hydrochloric acid converts thebaïne into an amorphous derivative, which is easily oxidized in the air and is soluble in alkalies.

Hesse,[48] who first obtained this body, called it *thebenine* and considered it as an isomer of thebaïne. Freund and his students [49] later investigated thebenine and found that its composition is $C_{18}H_{19}NO_3$, that it contains a methoxyl and a hydroxyl group and that it is a secondary base.

Distillation of thebenine with zinc-dust gives rise to *pyrene* and a base, *thebenidine*, $C_{15}H_9N$.[50]

On distilling the methyl hydroxide of thebaïne, Howard thought that he had obtained trimethylamine and a derivative of phenanthrene, $C_{14}H_{12}O_3$. Freund, on repeating Howard's experiment, showed that not trimethylamine was obtained, but *tetramethyl ethylene diamine*, a compound of nearly the same percentage composition:

$$(CH_3)_2{=}N{-}CH_2{-}CH_2{-}N{=}(CH_3)_2.$$

The formulæ of thebaïne and thebenine may then be represented as follows:

$(CH_3O)_2C_{16}H_{12}ONCH_3$	$(CH_3O)(OH)C_{16}H_{11}ONHCH_3$
Thebaïne	Thebenine

The experiment showing definitely a constitutional relation of thebaïne to morphine and codeïne is the action of acetic anhydride on the methyl iodide of thebaïne in the presence of silver acetate. Thebaïne is thus decomposed into a nitrogen-free compound, $C_{18}H_{16}O_4$, which proves to be the acetyl derivative

[48] Hesse, A. 153, 47.

[49] Freund and Göbel, B. 28, 941. Freund and Michaels, B. 30, 1357. Freund and Holthof, B. 32, 168.

[50] Vongerichten, B. 34, 767.

of a phenol, *thebaol*, $C_{16}H_{14}O_3$, and into a nitrogenous base, $C_4H_{11}NO$, which is identical with the *dimethyloxyethylamine*, $(CH_3)_2N—CH_2—CH_2—OH$, obtained from morphine and codeïne (page 273).

If thebaïne itself is treated with acetic anhydride, there are formed the acetyl derivative of thebaol and *methyloxyethylamine*, $CH_3HN—CH_2—CH_2OH$.

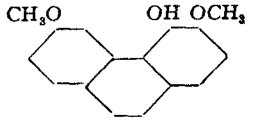
$$\underset{\text{Thebaïne}}{(CH_3O)_2C_{16}H_{12}ONCH_3} + H_2O \longrightarrow$$

$$\underset{\text{Thebaol}}{(CH_3O)_2C_{14}H_7OH} + \underset{\text{Methyloxyethylamine}}{HOC_2H_4NHCH_3}.$$

Thebaol (crystals melting at 94°) is a phenanthrene derivative; on distillation with zinc-dust it yields this hydrocarbon. Thebaol contains one hydroxyl and two methoxyl groups.

Oxidation with chromic acid converts it into *thebaol quinone*, $(CH_3O)_2{=}C_{14}H_5O_2—OH$, a derivative strikingly similar to phenanthraquinone. On further oxidation with potassium permanganate, thebaol quinone yields *o-methoxyphthalic acid*, $C_6H_3\begin{cases}OCH_3\\COOH\\COOH\end{cases}$, a result which indicates that the two methoxyl groups are not in *one* ring.

Thebaol is 4-*oxy*-3,6-*dimethoxyphenanthrene:*

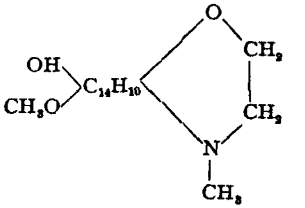


Thebaol

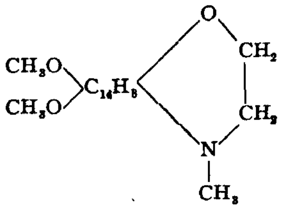
Its constitution is definitely established by the synthesis of thebaol quinone from 2-nitroisovanillin and the sodium salt of *p*-methoxyphenylacetic acid through a series of reactions such as were employed in the synthesis of methylmorphol quinone (page 275).[51]

[51] Pschorr, Seydel, and Stöhrer, B. 35, 4400.

The general behavior of thebaïne thus leads us to believe that it is not unlike morphine and codeïne in constitution. The two latter alkaloids are apparently derivatives of a tetrahydrophenanthrene; thebaïne, however, must be regarded as a derivative of a dihydrophenanthrene:

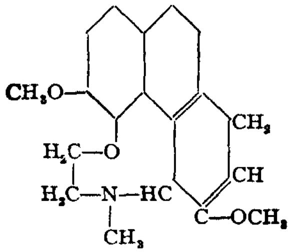


Codeïne



Thebaïne

Pschorr provisionally assigns to thebaïne the following formula:



Thebaïne

5. PAPAVERINE.

Papaverine was isolated by Merck [52] in 1848 and its empirical formula determined as $C_{20}H_{21}NO_4$. It crystallizes from benzol, or from a mixture of alcohol and ether, in prisms which melt at 147°; it is insoluble in water and alkalies, little soluble in alcohol, ether, and benzol, but somewhat more soluble in chloroform. Papaverine is a weak tertiary base without action on litmus; it is optically inactive. Its narcotic properties are quite feeble.

[52] Merck, A. 66, 125; 72, 50.

The constitution of this alkaloid was determined by the important investigations of Goldschmiedt,[53] which were published in the years 1883–1889. Papaverine was shown to be a derivative of *isoquinoline*—a result of considerable importance, since up to that time this ring had not been detected in any natural alkaloid.

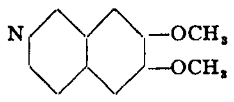
The following considerations led to the establishing of the constitution of papaverine:

1. Heated with hydriodic acid, papaverine yields four molecules of methyl iodide and a body of the formula $C_{16}H_{13}NO_4$, *papaveroline*, which is soluble in alkalies and easily oxidized. Papaverine, consequently, contains four methoxyl groups.

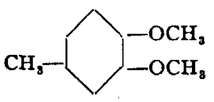
By careful saponification of papaverine one and two methyl groups may be eliminated, thus giving rise to tri- and di-methylpapaveroline.[54]

2. When papaverine is heated with very concentrated hydrochloric acid to 130°, it is decomposed, forming methyl chloride and homopyrocatechin, $C_6H_3CH_3(_1)(OH)_2(_{3,4})$.

3. On fusion with alkali, it yields a nitrogenous derivative, $C_{11}H_{11}NO_2$, *dimethoxylisoquinoline*,



and the nitrogen-free *dimethylhomopyrocatechin*,



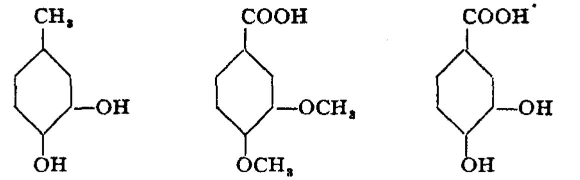
This last reaction is of particular interest.

In the fusion with alkali there are formed, in addition to dimethylhomopyrocatechin, the decomposition- and oxidation-

[53] Goldschmiedt, M. 4, 714; 6, 372, 667, 954; 7, 485; 8, 510; 9, 42, 327, 349, 762, 778; 10, 156, 673, 692; 13, 697; 17, 491.

[54] Pictet and Kramers, *Arch. Sc. phys. nat. Genève*, [4] 15, 121.

products of the latter. Thus we find ***homopyrocatechin***, ***veratric acid***, and ***protocatechuic acid:***



Homopyrocatechin Veratric acid Protocatechuic acid

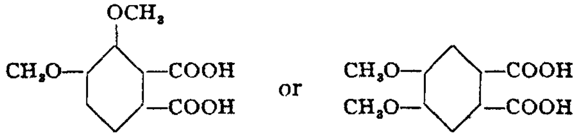
The primary decomposition-products of papaverine are, however, dimethoxylisoquinoline and dimethylhomopyrocatechin.

The former of these was at first regarded by Goldschmiedt as a dimethoxyquinoline, but its oxidation-products soon showed that it was an isoquinoline derivative. On oxidation it yields two acids, cinchomeronic acid (page 62) and a dibasic, dimethoxylated acid of the formula $C_6H_2(OCH_3)_2(COOH)_2$. The latter, which melts at 174–175°, is an isomer of hemipinic acid (page 306) and was called by Goldschmiedt *metahemipinic acid.*

Metahemipinic is a derivative of phthalic acid; its constitution was established as follows:

The acid readily yields an anhydride and an imide; the two carboxyls are accordingly in the ortho-position.

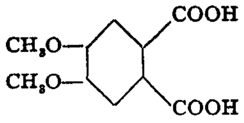
By fusion with caustic potash, it forms pyrocatechin; this indicates that the two methoxyl groups are attached to adjacent carbon atoms. Metahemipinic must consequently possess one of the two following formulæ:



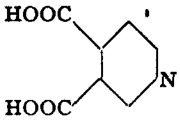
Metahemipinic acid

Now, as we shall show later, the first of these formulæ represents hemipinic acid, the oxidation-product of narcotine; the second formula must accordingly be assigned to metahemipinic acid.

The base, $C_{11}H_{11}NO_2$, giving rise by oxidation to metahemipinic and cinchomeronic acids,

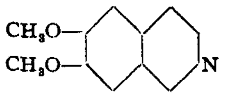


Metahemipinic acid



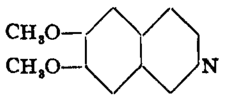
Cinchomeronic acid

must then be a *dimethoxylisoquinoline* of the following formula:

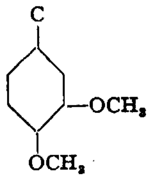


This behavior of dimethoxylisoquinoline on oxidation is exactly analogous to that of isoquinoline, which on like treatment yields phthalic and cinchomeronic acids.

The papaverine molecule is thus formed by the union of dimethoxylisoquinoline,



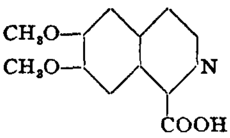
with the complex presented by dimethylhomopyrocatechin,



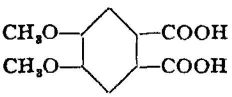
The mode in which these two groups are united has also been determined by Goldschmiedt. Papaverine possesses four methoxyl groups; each of the two decomposition-products also contains two such groups intact; consequently none of the methoxyl groups serves as the connecting link. The dimethylpyrocatechin complex must then be attached to the other either through the

carbon atom of the methyl group or through a like atom of the benzol nucleus. The investigations of Königs and Nef[55] favor the former attachment.

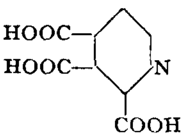
At which carbon atom of the isoquinoline complex does the union take place? This question is answered by the behavior of papaverine on oxidation with potassium permanganate. There are thus formed in addition to a large number of well-defined compounds (veratric acid, metahemipinic acid, metahemipinimide, *papaveraldine*, $C_{20}H_{19}NO_5$, *papaveric acid*, $C_{16}H_{13}NO_7$) α-carbocinchomeronic acid and a monobasic acid, $C_{12}H_{12}NO_4$, which proved to be the α-carboxyl derivative of dimethoxylisoquinoline. Further oxidation converts this last acid into metahemipinic acid and *α-carbocinchomeronic acid* (page 67):



Dimethoxylisoquinoline carboxylic acid

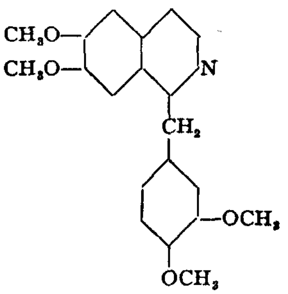


Metahemipinic acid

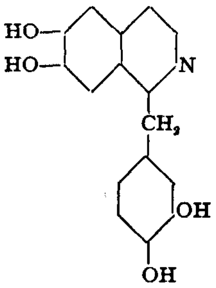


α-Carbocinchomeronic acid

It is evident from the above that the point of union in the isoquinoline complex is the α-carbon atom indicated. The constitution of papaverine and papaveroline may then be formulated as follows:



Papaverine



Papaveroline

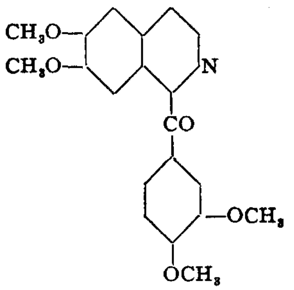
[55] Königs and Nef, B. 20, 622.

Of the oxidation-products of papaverine mentioned above we shall consider briefly papaveraldine and papaveric acid.

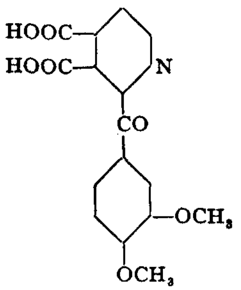
Papaveraldine, $C_{20}H_{19}NO_5$, differs from papaverine in possessing one more oxygen and two less hydrogen atoms. It forms crystals which melt at 210° and are insoluble in water and alkali. It reacts both with hydroxylamine and phenylhydrazine. Fused with potassium hydroxide, it is decomposed into veratric acid and dimethoxylisoquinoline.

Papaveric acid, $C_{16}H_{13}NO_7$, crystallizes with one molecule of water in plate-like crystals (melting-point 233°). It is a dibasic acid which yields an anhydride and from its reactions evidently contains a ketone group. It possesses two methoxyl groups; fused with alkalies it is converted into protocatechuic acid.

The constitution of these two derivatives is the following:



Papaveraldine



Papaveric acid

On reduction with zinc and acetic acid papaveraldine is converted into *papaverinol*, $C_6H_3(OCH_3)_2CH(OH)C_9H_4N(OCH_3)_2$ (colorless, monoclinic crystals).[56]

Papaverine contains no asymmetric carbon atom and is consequently optically inactive.

By the reduction of papaverine, however, Goldschmiedt obtained a *tetrahydropapaverine*, in which the pyridine nucleus is reduced:

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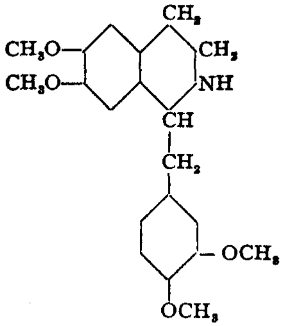
[56] Stuchlik, M. 21, 813.



This derivative, according to its constitution, possesses an asymmetric carbon atom. Pope and Peachey[57] have, indeed, succeeded in separating it into its two optical isomers through the salts formed with dextro-bromcamphor sulphonic acid.

6. CODAMINE,

$C_{20}H_{25}NO_4$, or $C_{18}H_{18}NO(OH)(OCH_3)_2$. This alkaloid was discovered by Hesse[58] in 1870. It crystallizes from ether in prisms which melt at 126° and which are little soluble in water, but readily soluble in organic solvents.

Its solubility in alkalies indicates the presence of a hydroxyl group. By Zeisel's method it can be shown that there are two methoxyl groups present.

7. LAUDANINE,

$C_{20}H_{25}NO_4$, or $C_{17}H_{15}N(OH)(OCH_3)_3$. Laudanine was also discovered by Hesse[58] in 1870. It crystallizes from alcohol, or from chloroform in prisms, melting at 166°. It is easily soluble in benzol, chloroform, and alkalies, little soluble in alcohol and ether. It is optically inactive and acts as a strong tetanic poison.

It contains a hydroxyl and three methoxyl groups and on

[57] Pope and Peachey, Proc. Soc., 1897–98, 122.
[58] Hesse, A. 153, 53; 282, 208; Supp. 8, 272.

oxidation with potassium permanganate yields metahemipinic acid.[59]

According to Hesse[60] inactive laudanosine (see below) is the monomethyl ether of laudanine. Laudanine would then be a *n-methyl-trimethylpapaveroline.*

8. LAUDANIDINE,

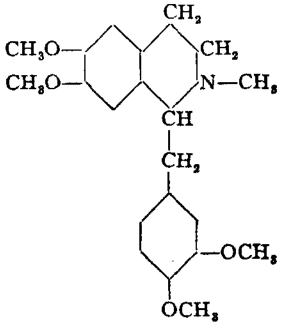
$C_{20}H_{25}NO_4$, or $C_{17}H_{15}N(OCH_3)_4$. Laudanidine was discovered by Hesse[61] in 1894. It contains three methoxyl groups, is lævorotatory, and melts at 177°. It closely resembles laudanine and is probably its lævo-modification.

9. LAUDANOSINE,

$C_{21}H_{27}NO_4$, or $C_{17}H_{15}N(OCH_3)_4$. This alkaloid was isolated by Hesse[62] in 1871. It crystallizes in needles melting at 89°; it is soluble in alcohol, ether, and chloroform; insoluble in water and alkali. It is dextrorotatory; it is a strong poison, producing tetanic convulsions.

The alkaloid possesses four methoxyl groups.

Pictet and Athanasescu[63] have shown that laudanosine is *dextro-n-methyl-tetrahydropapaverine:*



Laudanosine

[59] Goldschmiedt, M. 13, 691.
[60] Hesse, J. pr. [2] 65, 42.
[61] Hesse, A. 282, 208.
[62] Hesse, A. Suppl. 8, 318.
[63] Pictet and Athanasescu, B. 33, 2346; C. r. 131, 689.

Reduction of the methyl chloride of papaverine with tin and hydrochloric acid suffices to convert this alkaloid into inactive laudanosine. The racemic mixture is separated into its active constituents by means of quinic acid.

10. TRITOPINE,

$C_{42}H_{54}N_2O_7$, or probably $(C_{21}H_{27}NO_3)_2O$. Tritopine was discovered by Kauder in 1890. It crystallizes from alcohol in prisms or from ether in small plates. It melts at 182°, is easily soluble in alkalies and in chloroform; litt e soluble in ether and ligroin. It is a diacid base, which in its reactions and without much doubt in its constitution closely resembles the three alkaloids just discussed.

11. MECONIDINE,

$C_{21}H_{23}NO_4$. This alkaloid as well as the two succeeding were isolated by Hesse[64] in 1870. It is amorphous; its melting-point 58°; it is insoluble in water, but easily soluble in the ordinary organic solvents and in alkalies.

12. LANTHOPINE,

$C_{23}H_{25}NO_4$. Lanthopine crystallizes from chloroform in small prisms which melt near 200°. It is only slightly soluble in alcohol, benzol, and ether, but more soluble in chloroform; it is dissolved by alkalies.

13. PROTOPINE.

Hesse, who discovered protopine, assigned to it the formula $C_{20}H_{19}NO_5$. According to later investigations of Schmidt and Selle,[65] the alkaloid possesses the formula $C_{20}H_{17}NO_5$. Still

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[64] Hesse, A. 153, 47; Suppl. 8, 261.

[65] Schmidt and Selle, A. Pharm. 228, 441; 231, 136.

later Hopfgartner [66] returned to the formula of Hesse. Hesse's formula is also confirmed by Schmidt.[67]

Protopine crystallizes from ether or chloroform in needles melting at 207°. It is insoluble in water and alkalies, very little soluble in alcohol, ether, and benzol, somewhat soluble in chloroform. It is a tertiary base, optically inactive. The alkaloid is probably identical with *macleyine*, which was discovered by Eykman [68] in 1885 in the roots of *Macleya cordata*, R. Br. (family of the Papaveraceæ).

14. CRYPTOPINE,

$C_{21}H_{23}NO_5$, or $C_{19}H_{17}NO_3(OCH_3)_2$. Cryptopine was discovered by T. and H. Smith [69] in 1857 and was investigated by Hesse.[70] It crystallizes from alcohol or ether in prisms melting at 213°. It is insoluble in water and alkalies, little soluble in alcohol, ether, and benzol. It is optically inactive and acts physiologically as a narcotic.

Cryptopine is apparently closely related to protopine. It contains two methoxyl groups; on oxidation with potassium permanganate it yields metahemipinic acid.

15. PAPAVERAMINE,

$C_{21}H_{21}NO_6$. Papaveramine was discovered by Hesse [71] in 1886. It forms prisms which melt at 142°; it is easily soluble in alcohol and chloroform, little soluble in ether, and insoluble in water and alkalies.

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[66] Hopfgartner, M. 19, 179.
[67] Schmidt, *Central-Blatt*, 1901, II, 781.
[68] Eykman, R. 3, 182.
[69] T. and H. Smith, *Pharmaceutical Journal*, [2] 8, 595, 716.
[70] Hesse, A. Suppl. 8, 299; 176, 200.
[71] Hesse, J. 1886, 1721.

16. NARCOTINE.

Narcotine was isolated by Robiquet[72] in 1817. It occurs in opium (0.75–9.6%) in the free condition and may be obtained by simple extraction with ether. Its empirical formula as determined by Matthiessen and Foster[73] is $C_{22}H_{23}NO_7$.

The alkaloid separates from an alcoholic or ethereal solution in prisms which melt at 176°. It is insoluble in cold water, little soluble in hot, somewhat more soluble in alcohol and ether; it dissolves readily in benzol and chloroform. It is a weak tertiary base, little poisonous. In neutral solution it is lævorotatory, in acid it turns the plane of polarized light to the right.[74]

Narcotine is in the cold insoluble in alkalies; on being heated, however, it dissolves, forming unstable salts, *narcotates*.[75] These salts are readily decomposed by acids or by hot water; they are formed from narcotine by the addition of a molecule of water, a lactone ring being thus opened. Narcotine itself does not contain a hydroxyl group; it is unaffected both by acetic anhydride and acetyl chloride.[76]

The action of hydrochloric and hydriodic acids indicates the presence of three methoxyl groups. On being heated with one of these acids, narcotine yields in succession the following bodies:

Dimethylnornarcotine, $C_{19}H_{14}NO_4(OH)(OCH_3)_2$,
Methylnornarcotine, $C_{19}H_{14}NO_4(OH)_2(OCH_3)$,
Nornarcotine, $C_{19}H_{14}NO_4(OH)_3$.

These are amorphous derivatives, easily oxidized and soluble in alkalies even in the cold.[77]

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[72] Robiquet, A. ch. [2] 5, 575.
[73] Matthiessen and Foster, A. Suppl. 1, 330; Suppl. 2, 337; Suppl. 5, 332.
[74] Hesse, A. 176, 192.
[75] Wöhler, A. 50, 25. Hesse, A. 176, 192.
[76] Beckett and Wright, Soc. 29, 167.
[77] Matthiessen, A. Suppl. 7, 59.

When narcotine is heated alone, or is subjected to the action of water at 250°, or of barium hydroxide or the caustic alkalies at 220°, it is decomposed, yielding methylamine, dimethylamine, and trimethylamine. This appears to indicate the presence of a *n*-methyl group—an indication which has been confirmed by the process of Herzig and Meyer.[78]

When heated with acetic acid to 130°, narcotine is converted, according to T. and H. Smith,[79] into an isomer, ***gnoscopine*** (page 311).

When the methyl iodide of narcotine is heated with alkalies it yields *narceïne* (page 311).[80]

Phenylhydrazine is without action on narcotine.

Heated with water at 140°, or with sulphuric acid, or with baryta-water, the alkaloid is decomposed into a non-nitrogenous acid, ***opianic acid***, and a base, ***hydrocotarnine:***[81]

$$\underset{\text{Narcotine}}{C_{22}H_{23}NO_7} + H_2O \longrightarrow \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydrocotarnine}}{C_{12}H_{15}NO_3}.$$

By reducing agents, such as zinc and hydrochloric acid or sodium amalgam, a similar decomposition is effected; in this case, however, instead of opianic acid, there is obtained its reduction-product, ***meconine:***[81]

$$\underset{\text{Narcotine}}{C_{22}H_{23}NO_7} + 2H \longrightarrow \underset{\text{Meconine}}{C_{10}H_{10}O_4} + \underset{\text{Hydrocotarnine}}{C_{12}H_{15}NO_3}.$$

When narcotine is oxidized with various reagents, such as nitric acid, chromic acid, etc., it yields ***opianic acid*** and ***cotarnine:***[82]

$$\underset{\text{Narcotine}}{C_{22}H_{23}NO_7} + H_2O + O \longrightarrow \underset{\text{Opianic acid}}{C_{10}N_{10}O_5} + \underset{\text{Cotarnine}}{C_{12}H_{15}NO_4}.$$

[78] Herzig and Meyer, M. **15**, 613.

[79] T. and H. Smith, *Pharmaceutical Journal*, **52**, 794.

[80] Roser, A. **247**, 167; B. **32**, 2974. Freund and Frankforter, A. **277**, 20. Frankforter and Keller, Am. Chem. Jour., **22**, 61.

[81] Beckett and Wright, Soc. **28**, 583.

[82] Wöhler, A. **50**, 1. Blyth, A. **50**, 29. Anderson, A. **86**, 44, 163. Matthiessen and Wright, A. Suppl. **7**, 63. Kerstern, J. 1889, 2000.

In addition to these two products there is also often formed hemipinic acid, $C_{10}H_{10}O_6$, which results from the further oxidation of opianic acid.

The molecule of narcotine accordingly consists of two atomic groupings: the nitrogenous one is contained in cotarnine, $C_{12}H_{15}NO_4$, and hydrocotarnine, $C_{12}H_{15}NO_3$; the other free from nitrogen is found in the derivatives meconine, $C_{10}H_{10}O_4$, opianic acid, $C_{10}H_{10}O_5$, and hemipinic acid, $C_{10}H_{10}O_6$.

Liebermann[83] attempted to synthesize narcotine from its decomposition-products, hydrocotarnine and opianic acid:

$$C_{12}H_{15}NO_3 + C_{10}H_{10}O_5 \rightarrow C_{22}H_{23}NO_7 + H_2O.$$

By adding an equimolecular mixture of these two bodies to 73% sulphuric acid, condensation is indeed effected, but the product obtained differs from narcotine. This new derivative, *isonarcotine*, melts at 194°, is optically inactive and could not be separated by dextro-tartaric acid into optically active constituents.[84] It is soluble in hot benzol, difficultly so in ether; in water, ammonia, and alkalies it is insoluble. Unlike narcotine, it gives with concentrated sulphuric acid a characteristic red coloration. It possesses no particular physiological action.

We shall now examine the structure of the different decomposition-products of narcotine and shall then present the conclusions which naturally follow regarding the constitution of the alkaloid itself.

Cotarnine.—In 1844 Wöhler[85] first obtained this derivative by treating narcotine with manganese dioxide and sulphuric acid and assigned to it the formula $C_{13}H_{13}NO_3$. Later the formula $C_{12}H_{13}NO_3 + H_2O$, proposed by Matthiessen and Foster,[86] appeared to be more acceptable. More recent investigations of Roser[87] have, however, shown that the supposed water of crystal-

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[83] Liebermann, B. 29, 183, 2040.
[84] Bandow, B. 30, 1745.
[85] Wöhler, A. 50, 1.
[86] Matthiessen and Foster, A. Suppl. 1, 330.
[87] Roser, A. 249, 156.

lization is in reality water of constitution and that consequently the formula for free cotarnine is $C_{12}H_{15}NO_4$. Its salts, however, bear the formulæ $C_{12}H_{13}NO_3 \cdot HCl$, $(C_{12}H_{13}NO_3)_2H_2SO_4$, etc., and are consequently formed by the elimination of a molecule of water.

Cotarnine crystallizes from benzol in needles and melts with decomposition at 132–133°. It is weakly alkaline in reaction and is non-poisonous. It is almost insoluble in water and alkalies, but is readily soluble in alcohol and ether.

It is a secondary base and forms by the action of benzoyl chloride and sodium hydroxide a benzoyl derivative. Its aldehyde character is shown by its reaction with hydroxylamine [88] and prussic acid.[89]

It contains a methoxyl group, as is shown by the elimination of methyl chloride or iodide when the base is heated to 140° with the corresponding halogen acid.[90]

Reduction converts cotarnine into hydrocotarnine.

The first indications regarding the constitution of cotarnine were given by its behavior on oxidation.

On treating the base with nitric acid or manganese dioxide and sulphuric acid, Wöhler and Anderson obtained a monobasic acid, $C_8H_7NO_4$, to which the first of these investigators, on account of the resemblance of its crystal form to that of apophyllite, gave the name *apophyllenic acid*. This derivative crystallizes from water in prisms containing a molecule of water; it melts with decomposition at 241°, is difficultly soluble in cold water, almost insoluble in alcohol and ether.

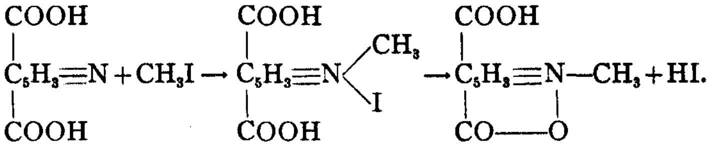
The study of apophyllenic acid was taken up anew in 1880 by von Gerichten.[91] This investigator noted that when the acid is heated with hydrochloric acid to 250° it is decomposed into methyl chloride and cinchomeronic acid (page 62):

$$\underset{\text{Apophyllenic acid}}{C_8H_7NO_4} + HCl \rightarrow \underset{\text{Cinchomeronic acid}}{C_7H_5NO_4} + CH_3Cl.$$

[88] Roser, A. 249, 156; 254, 334.
[89] Freund and Preuss, B. 33, 380. Freund and Bamberg, B. 35, 1739.
[90] Matthiessen and Foster, A. Suppl. 2, 379.
[91] von Gerichten, A. 210, 79.

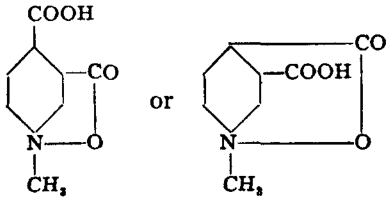
Apophyllenic acid is a monobasic acid and it seemed natural from the foregoing reaction to regard the acid as the mono-methyl ester of cinchomeronic acid, $C_5H_3N(COOH)(COOCH_3)$. But von Gerichten was compelled to forego this interpretation, since apophyllenic acid could not be converted by saponification with alkalies into cinchomeronic acid. It only remained then to look upon apophyllenic acid as a betaïne derivative (page 73).

This view was confirmed by the synthesis of the acid, which was effected by Roser[92] in 1886 by heating cinchomeronic acid with methyl iodide at the temperature of the water-bath:



Cinchomeronic acid — Methyl iodide of cinchomeronic acid — Apophyllenic acid

Apophyllenic acid is accordingly the methylbetaïne of cinchomeronic acid:



The evidence, however, is as yet scarcely sufficient to determine which of these formulæ correctly represents the constitution of the acid, although possibly preference is to be given to the first.[93]

The presence of a pyridine ring in the molecule of cotarnine was also shown by the action of bromine on the base; there are thus obtained pyridine derivatives. Beckett and Wright[94] isolated

[92] Roser, A. 234, 116.
[93] Kirpal, M. 23, 239, 765; 24, 519. Kaas, M. 23, 250, 681.
[94] Beckett and Wright, Soc. 28, 580; 29, 169; 32, 531.

as the first product of this reaction a derivative, $C_{12}H_{13}Br_4NO_3$, which, on being heated to 200°, was decomposed into methyl bromide (one molecule), hydrobromic acid (two molecules), and a substance, *bromtarconine*, $C_{11}H_8BrNO_3$ (orange-yellow needles, melting at 235–238°).

Now when bromtarconine is distilled over soda-lime it yields pyridine, and when oxidized with chromic acid it is converted into apophyllenic acid.[95]

If bromtarconine is treated with bromine there is formed among other derivatives *dibromapophylline*, $(C_7H_5Br_2NO_2)_2$. When this substance is heated with hydrochloric acid to 200°, it is decomposed into carbon dioxide, methyl chloride, and $\beta\beta'$-dibrompyridine (page 16).

The further solution of the constitution of cotarnine we owe to the investigations of Roser,[96] who applied to the base the exhaustive methylation of Hofmann.

Since cotarnine is a secondary base, it unites with two molecules of methyl iodide to form a methyl iodide of *methylcotarnine.*

When this derivative is heated with caustic soda it is decomposed into trimethylamine and a nitrogen-free substance, *cotarnone.* The formation of trimethylamine after the absorption of only two molecules of methyl iodide shows that cotarnine must possess a *n*-methyl group. Since cotarnine is a secondary base there must be present the atomic grouping NH—CH_3; the base, consequently, cannot contain a pyridine ring.

$$\underset{\text{Cotarnine}}{C_{11}H_{11}O_4\text{—NH—}CH_3} + 2CH_3I \rightarrow \underset{\text{Methyliodide of methylcotarnine}}{C_{11}H_{11}O_4\text{—}N(CH_3)_3I} + HI$$

$$C_{11}H_{11}O_4\text{—}N(CH_3)_3I + NaOH \rightarrow \underset{\text{Cotarnone}}{C_{11}H_{10}O_4} + N(CH_3)_3 + NaI + H_2O.$$

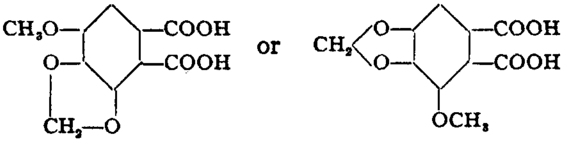
Cotarnone crystallizes from alcohol in leaflets which melt

[95] von Gerichten, B. **13**, 1635; **14**, 310; A. **210**, 79; **212**, 165.
[96] Roser, A. **249**, 156; **254**, 334; *Chemiker-Zeitung*, **20**, 782.

at 78°. It adds two atoms of bromine and likewise forms an oxime; it thus appears to contain an ethylene bond and an aldehyde or ketone group.

Cotarnone proves to be a derivative of gallic acid, and this affords us an insight into the probable constitution of cotarnine itself.

Oxidation with potassium permanganate converts cotarnone into a dibasic acid, *cotarnic acid*, $C_8H_6O_2(COOH)_2$ (leaflets melting at 178°). This acid Roser regarded as a *methyl-methylene-trioxyphthalic acid:*

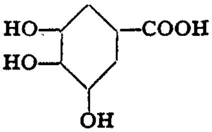


The following three observations lead to this constitutional formula for cotarnic acid:

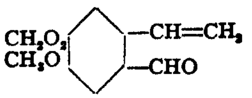
1. The two carboxyls are in an *ortho*-position, since cotarnic acid forms an anhydride.

2. The presence of a methoxyl group is shown by the method of Zeisel.

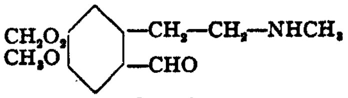
3. On being heated with hydriodic acid and phosphorus, cotarnic acid is converted into *gallic acid:*



From the above formulæ for cotarnic acid we derive the following for cotarnone and cotarnine:

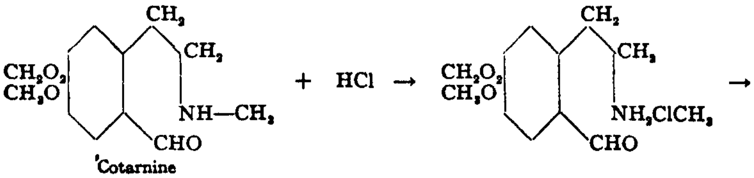


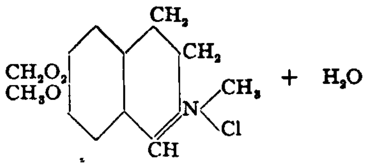
Cotarnone



Cotarnine

According to this formula free cotarnine does not contain a pyridine ring; in the conversion to its salts, however, such a ring is formed. We have seen that the salts of this alkaloid are not formed by the simple addition of an acid, as is ordinarily the case, but that there is at the same time a loss of a molecule of water. It is this loss of water which brings about the union of the aldehyde carbon atom with the nitrogen atom and thus leads to the formation of a pyridine nucleus:





Cotarnine hydrochloride

The salts of cotarnine are accordingly quaternary derivatives of a *dihydroisoquinoline.*

From a study of the absorption-spectra of cotarnine and its salts, Dobbie, Lauder, and Tinkler[97] believe that the free base passes into the quaternary ammonium form when dissolved in alcohol.

The formation of cotarnic and apophyllenic acids by the oxidation of cotarnine in acid solution is thus entirely analogous to that of phthalic and cinchomeronic acids by the oxidation of isoquinoline:

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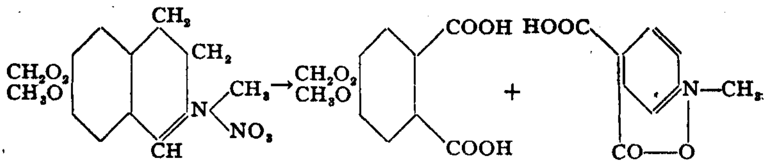
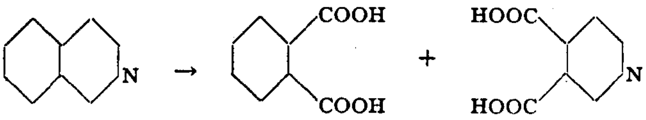
[97] Dobbie, Lauder, and Tinkler, Proc. Soc. 19, 75; Soc. 83, 598.

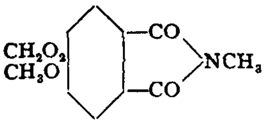


Cotarnine nitrate — Cotarnic acid — Apophyllenic acid

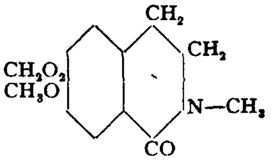


Isoquinoline — Phthalic acid — Cinchomeronic acid

By the oxidation of cotarnine with potassium permanganate, there are formed, in addition to small quantities of potassium cotarnate, the *methylimide of cotarnic acid* and *oxycotarnine:*[98]



Methylimide of cotarnic acid



Oxycotarnine

Hydrocotarnine, $C_{12}H_{15}NO_3$.—Hydrocotarnine is formed, as has already been indicated (page 297), by the decomposition of narcotine. It crystallizes in prisms which contain one-half molecule of water and melt at 55°; it may be distilled with but slight decomposition; it is readily soluble in organic solvents, insoluble in water and alkalies. The base is optically inactive and is more poisonous than cotarnine and narcotine.

The constitution of hydrocotarnine follows from its formation by the reduction of cotarnine either by electrolysis or by means of zinc and hydrochloric acid.[99] On the other hand, oxidation converts hydrocotarnine into cotarnine.

Hydrocotarnine is a tertiary base. At first glance it may appear strange that a secondary base like cotarnine would on

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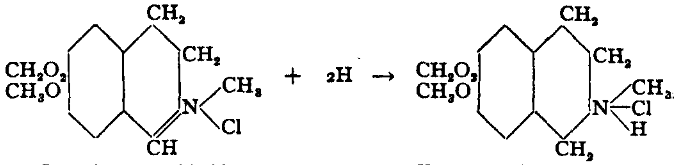
[98] Freund and Wulff, B. 35, 1737.

[99] Beckett and Wright, Soc. 28, 577. Bandow and Wolffenstein, B. 31, 1577.

reduction yield a tertiary. This reaction becomes clear, however, if we consider the reduction as affecting the salts of cotarnine and not the free base:



Cotarnine hydrochloride — Hydrocotarnine hydrochloride

Hydrocotarnine is thus a derivative of *methyltetrahydroisoquinoline.*

By the action of sulphuric acid hydrocotarnine forms a condensation-product, hydrodicotarnine, $C_{24}H_{28}N_2O_6$. This crystallizes in light-yellow needles which melt at 211° and unlike hydrocotarnine are insoluble in ammonia.[100]

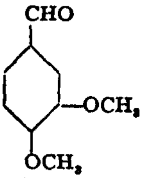
Opianic Acid, $C_{10}H_{10}O_5$.—Opianic acid crystallizes in prisms which melt at 150°. It is little soluble in cold water, but readily soluble in alcohol and ether. It shows the properties both of a monobasic acid and of an aldehyde. It possesses two methoxyl groups, since two molecules of methyl chloride or iodide are evolved by the action of the corresponding halogen acid. In this reaction there are also formed the following two derivatives:[101]

Methylnoropianic acid, $C_9H_8O_5$
Noropianic acid, $C_8H_6O_5$.

The formula of opianic acid may accordingly be represented as $C_6H_2(OCH_3)_2(CHO)(COOH)$.

The position of the two methoxyl groups in their relation to the aldehyde group is shown by the formation of *methylvanillin,* when opianic acid is distilled with soda-lime:[102]

[100] Bandow, B. 30, 1745.
[101] Matthiessen and Foster, J. 1867, 519. Wright, J. 1877, 770.
[102] Beckett and Wright, J. 1876, 807. Liebermann and Chojnacki, B. 4, 194; A. 162, 323.



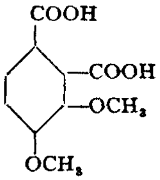
Methylvanillin

In what position now must the carboxyl group be introduced to obtain opianic acid? This question finds answer in a study of the oxidation and reduction-products of opianic acid.

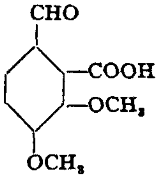
The oxidation of the acid (by means of lead peroxide, nitric acid, chromic acid, or platinum chloride) converts it into the well-known, dibasic *hemipinic acid.*

On reduction with sodium amalgam, or zinc and sulphuric acid, opianic acid yields *meconine.*

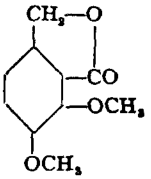
These reactions indicate that the three substances bear to one another the relation of acid, aldehyde, and alcohol:



Hemipinic acid

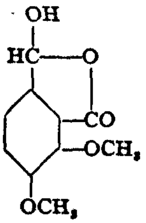


Opianic acid



Meconine

Opianic acid frequently reacts in its tautomeric form as an oxyphthalide derivative:[103]

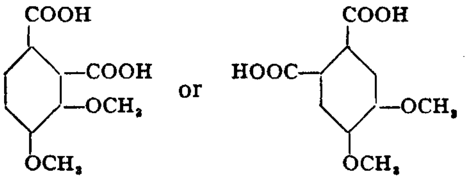


Hemipinic Acid, $C_{10}H_{10}O_6$.—This acid, which is formed not only by the oxidation of opianic acid and of narcotine but

[103] Liebermann, B. 19, 765, 2288.

also by that of several other alkaloids (oxynarcotine, narceïne, hydrastine, berberine), crystallizes in prisms containing a varying quantity of water (½–2½ molecules). The anhydrous acid melts near 180° and can be sublimed. It is little soluble in water, somewhat soluble in alcohol, and very readily soluble in ether.

Hemipinic acid is a dibasic acid, $C_8H_8O_2(COOH)_2$, which on being heated is converted into its anhydride.[104] This fact, in connection with those which determine the position of the three substituents in opianic acid, limits the constitution of hemipinic acid to the two following possibilities:



I II

The choice between these two formulæ was neatly determined by Wegscheider.[105] It will be apparent at a glance that a derivative of the first formula can yield two different ester acids, while one of the second formula can form but one such ester acid, since in the second formula the two carboxyls are symmetrically arranged with reference to the rest of the molecule. Now Wegscheider succeeded in obtaining two monomethyl esters of hemipinic acid, the one, the α-ester, by oxidation of the methyl ester of opianic acid, the other, the β-ester, by treating a methyl alcohol solution of hemipinic acid with hydrogen chloride.

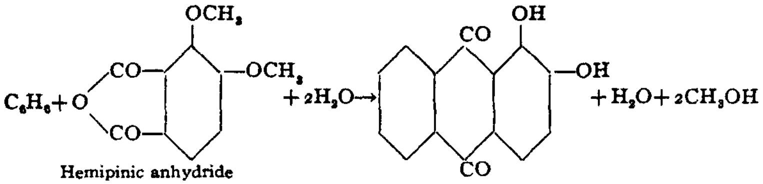
Hemipinic acid possesses, accordingly, the former of the above formulæ.

This result has also been confirmed by an observation of Lagodzinski.[106]

This investigator obtained alizarine by the condensation

[104] Prinz, J. pr. [2] 24, 370.
[105] Wegscheider, M. 3, 384; 4, 262.
[106] Lagodzinski, B. 28, 1427.

of hemipinic anhydride with benzol in the presence of aluminum chloride and the subsequent treatment of the condensation-product with concentrated sulphuric acid:



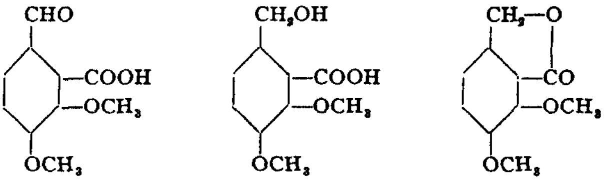
Hemipinic anhydride Alizarine

Meconine, $C_{10}H_{10}O_4$.—Meconine, the reduction-product of opianic acid, is found in small quantities (0.05–0.08%) in opium, where it was discovered by Dublanc[107] in 1832. It has also been found in the roots of *Hydrastis canadensis* L. (page 315).[108]

Meconine forms prisms which melt at 102.5° and sublime without decomposition; it is easily soluble in alcohol, ether, benzol, and chloroform, little soluble in water; it is optically inactive.

With alkalies, meconine yields soluble salts of a monobasic acid, *meconinic acid*, $C_{10}H_{12}O_5$; the acid itself is not stable and is reconverted into meconine when an attempt is made to precipitate it from its salt solutions.[109]

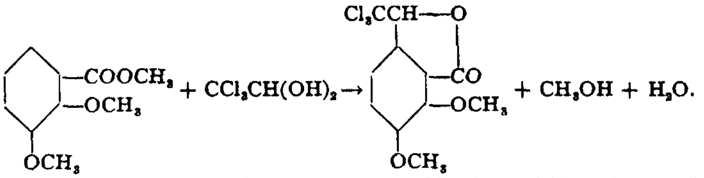
These properties indicate that meconinic acid is the alcohol corresponding to opianic acid and that meconine is the corresponding lactone of the phthalide form:



Opianic acid Meconinic acid Meconine

[107] Dublanc, A. ch. [2] 49, 17.
[108] Freund, B. 22, 456; A. 271, 311.
[109] Hessert, B. 11, 240.

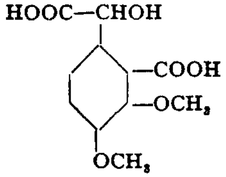
Fritsch[110] has succeeded in synthesizing meconine. By the condensation of the methyl ester of 2,3-*dimethoxybenzoic acid* and *chloral hydrate* (molecular quantities) by means of concentrated sulphuric acid there is formed 5,6-*dimethoxy-trichlormethylphthalide:*



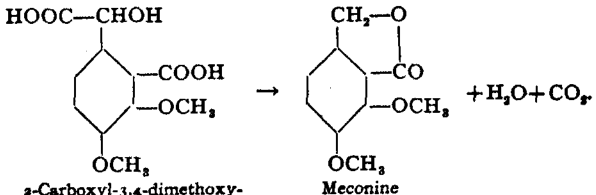
The methyl ester of 2,3-dimethoxy-benzoic acid

5,6-Dimethoxy-trichlormethylphthalide

On saponification with sodium hydroxide, this yields 2-*carboxyl*-3,4-*dimethoxymandelic acid:*



which on being heated loses water and carbon dioxide and forms meconine:



2-Carboxyl-3,4-dimethoxy-mandelic acid

Meconine

Attempts to prepare meconine by the reduction of hemipinic anhydride with zinc and acetic acid led to an isomer of meconine, *pseudomeconine:*[111]

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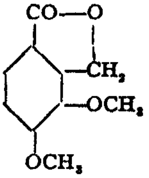
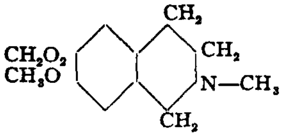
[110] Fritsch, A. 301, 352.
[111] Salomon, B. 20, 883.

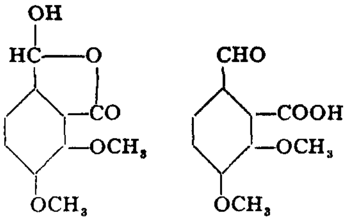


Pseudomeconine

Constitution of Narcotine.—As we have seen (page 297) narcotine decomposes with the absorption of water into opianic acid and hydrocotarnine. The constitutional formulæ of these two decomposition-products we have found to be represented as follows:



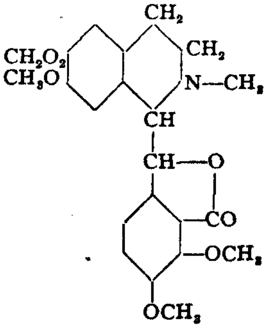
Hydrocotarnine



Opianic acid (Oxyphthalide form) Opianic acid

It remains only to determine in what way these complexes are united to form the narcotine molecule.

Now, since narcotine is a tertiary base and contains neither a carboxyl nor an aldehyde group, it is highly probable that the formula for narcotine should be represented as follows:



Narcotine

17. Gnoscopine.

This alkaloid was isolated from opium by T. and H. Smith[112] in 1878. It bears the formula $C_{22}H_{23}NO_7$ and is accordingly isomeric with narcotine, probably steroisomeric.

The absorption-spectra of the two alkaloids are identical.[113]

According to the directions of Smith it is formed by heating narcotine with acetic acid to 130°.

Gnoscopine crystallizes from alcohol in needles which melt at 228°; it is readily soluble in benzol and chloroform, little soluble in alcohol, insoluble in water and alkalies.

18. Oxynarcotine.

This alkaloid, which was discovered by Beckett and Wright[114] in 1875, possesses the formula $C_{22}H_{23}NO_8$. It forms a crystalline powder, little soluble in alcohol and hot water, and almost insoluble in ether, chloroform, and benzol.

In its constitution, oxynarcotine is without doubt closely related to narcotine; it differs from this alkaloid, indeed, only by an atom of oxygen. Treated with ferric chloride, it is decomposed into cotarnine and hemipinic acid:

$$\underset{\text{Oxynarcotine}}{C_{22}H_{23}NO_8} + H_2O + O \rightarrow \underset{\text{Cotarnine}}{C_{12}H_{15}NO_4} + \underset{\text{Hemipinic acid}}{C_{10}H_{10}O_6}.$$

Under the same conditions narcotine is decomposed into cotarnine and opianic acid, $C_{10}H_{10}O_5$.

19. Narceïne.

Narceïne was discovered by Pelletier[115] in 1832. It received from Anderson[116] the formula $C_{23}H_{29}NO_9 + 2H_2O$. According

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[112] T. and H. Smith, *Pharmaceutical Journal*, [3] 8, 415; 9, 81; 52, 794.

[113] Dobbie and Lauder, Soc. 83, 605.

[114] Beckett and Wright, Soc. 29, 461.

[115] Pelletier, A. ch. [2], 50, 252.

[116] Anderson, A. 86, 181.

to later investigations of Freund and Frankforter,[117] this formula must be altered to the expression $C_{23}H_{27}NO_8+3H_2O$.

Roser[118] succeeded in converting narcotine into narceïne by heating the methyl chloride of the former with alkali:

$$\underset{\text{Methyl chloride of narcotine}}{C_{22}H_{23}NO_7\cdot CH_3Cl}+NaOH \rightarrow \underset{\text{Narceïne}}{C_{23}H_{27}NO_8}+NaCl.$$

By the same treatment of the ethyl chloride of narcotine there is formed *homonarceïne*, $C_{24}H_{29}NO_8$.

Narceïne crystallizes from water or alcohol in prismatic needles, which in the hydrous condition melt at 170–171°, in the anhydrous at 145°. It is little soluble in cold alcohol and chloroform, still less soluble in water and insoluble in ether, benzol, and ligroin. It is a weak tertiary base, optically inactive.[119] Of all the opium alkaloids it is the strongest narcotic.[120]

Narceïne has no alcoholic hydroxyl group; it is unaffected by acetic anhydride. It possesses, however, three methoxyl groups and has two methyl groups attached to the nitrogen.[121] The latter observation is of importance, since it shows that narceïne contains no pyridine ring.

The alkaloid is soluble in alkalies; it is converted into an ester by alcohol and hydrochloric acid; this indicates the presence of a carboxyl group in the molecule. It possesses, furthermore, a CO group, since it reacts with hydroxylamine and phenylhydrazine.

Its formula may accordingly be resolved as follows

$$C_{16}H_{11}O_2\left(N\langle{}^{CH_3}_{CH_3}\right)(OCH_3)_3(CO)(COOH).$$

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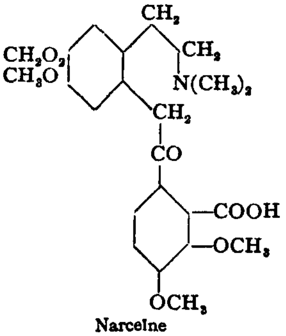
[117] Freund and Frankforter, A. 277, 20.
[118] Roser, A. 247, 167; B. 32, 2974.
[119] Hesse, A. 176, 198.
[120] von Schröder, *Archiv. für experimentelle Pathologie*, 1883, 132.
[121] Herzig and Meyer, M. 16, 599.

Narceïne cannot be decomposed into two atomic groups, as has been effected in the case of narcotine. On oxidation with chromic acid, ferric chloride, or potassium permanganate, there is indeed obtained hemipinic acid, but no product analogous to cotarnine.[122]

The properties and reactions of narceïne, particularly its formation from the methyl chloride of narcotine, appear to be best expressed in the following constitutional formula, which has been proposed by Freund and Frankforter:



Narceïne

20. Hydrocotarnine.

Hesse[123] found this alkaloid in opium. It has already been discussed on page 304.

21. Xanthaline.

T. and H. Smith[124] isolated xanthaline from opium in 1893 and gave it the formula $C_{37}H_{36}N_2O_9$. It is a crystalline powder which melts at 206°; it is insoluble in water and alkalies, little

[122] Beckett and Wright, Soc. 29, 467.

[123] Hesse, A. Suppl. 8, 320.

[124] T and H. Smith, *Pharmaceutical Journal* 52 793.

soluble in boiling alcohol, more readily soluble in benzol and chloroform. Its salts are yellow in color.

On reduction with zinc and hydrochloric acid, xanthaline is converted into *hydroxanthaline*, $C_{37}H_{38}N_2O_9$. This melts at 137° and forms colorless salts.

CHAPTER XXV.

ALKALOIDS FROM HYDRASTIS CANADENSIS.

We include under this title a number of alkaloids which are found not only in the root of the golden seal, etc. (*Hydrastis canadensis* L., family of the Ranunculaceæ), but also in that of the common barberry (*Berberis vulgaris* L., family of the Berberidaceæ), and of a few other related species as *Nandina domestica*, Thumb. (the same family).

All these alkaloids appear to be more or less closely related in constitution. They include·

1. Hydrastine............. $C_{21}H_{21}NO_6$.
2. Berberine.............. $C_{20}H_{17}NO_4$.
3. Canadine.............. $C_{20}H_{21}NO_4$.
4. Nandinine.............. $C_{19}H_{19}NO_4$.
5. Oxyacanthine........... $C_{19}H_{21}NO_3$ or $C_{18}H_{19}NO_3$.
6. Berbamine............. $C_{18}H_{19}NO_3$.

The root of *Hydrastis canadensis* contains hydrastine (1½%), berberine (4%), and canadine, together with a small quantity of meconine; that of *Berberis vulgaris* contains berberine (1.3%), oxyacanthine, and berbamine; in that of *Nandina domestica* are found berberine and nandinine.

1. Hydrastine.

Hydrastine was observed by Durand[1] in 1851, but was first isolated in a pure condition by Perrins[2] in 1862. The first

[1] Durand, *Am. Jour. Pharm.* 23, 112.
[2] Perrins, *Pharmaceutical Journal,* [2] 3, 546.

formula assigned to the alkaloid was that of $C_{22}H_{23}NO_6$;[3] the later analyses of a number of investigators,[4] however, showed that this must be replaced by the expression $C_{21}H_{21}NO_6$.

Hydrastine is found in the rhizome of *Hydrastis canadensis*, partly in the free condition, partly in combination.[5]

The alkaloid crystallizes from its alcoholic solution in prisms which melt at 132° and which are insoluble in water, somewhat soluble in alcohol, and easily soluble in benzol and chloroform. It is a tertiary base of alkaline reaction and but little poisonous.

Hydrastine, like narcotine, is lævorotatory in neutral solution, dextrorotatory in acid.

The first observation bearing upon the molecular structure of this alkaloid was made by Power[6] in 1884. He noted that hydrastine on being fused with caustic potash is decomposed into protocatechuic and formic acids.

Then followed a long series of investigations by Freund and his students[7] and by E. Schmidt,[8] which have fully solved the constitution of hydrastine. The alkaloid is found to be closely related to narcotine; the latter, indeed, is most probably a methoxylhydrastine.

The following is a résumé of these investigations:

Hydrastine possesses two methoxyl groups (method of Zeisel). It does not react with hydroxylamine, nor with phenylhydrazine and it forms no addition-product with bromine; it accordingly contains no aldehyde or ketone group, nor is there an ethylene bond present.

On oxidation there are obtained almost the same derivatives as in the case of narcotine. Dilute nitric acid converts it into *apophyllenic acid* (page 299); potassium permanganate gives rise to *hemipinic acid;* chromic acid or manganese dioxide

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[3] Mahla, *Am. Jour. of Sci.* **86**, 57.

[4] Freund and Will, B. **20**, 88. Eykman, R. **5**, 291.

[5] Linde, A. Pharm. **236**, 696.

[6] Power, *Pharmaceutical Journal*, [3] **15**, 297.

[7] Freund, B. **19**, 2797; **20**, 88, 2400; **22**, 456, 1156, 2322, 2329; **23**, 404, 2897, 2910; **24**, 2730; **25**, Ref. 234; **26**, 2488; A. **271**, 311.

[8] Schmidt, A. Pharm. **224**, 974; **226**, 239; **228**, 49, 221, 596; **231**, 541; **232**, 136.

and sulphuric acid decompose it into opianic acid and a base, ***hydrastinine***, $C_{11}H_{13}NO_3$, which corresponds to cotarnine:

$$\underset{\text{Hydrastine}}{C_{21}H_{21}NO_6} + H_2O + O \rightarrow \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydrastinine}}{C_{11}H_{13}NO_3}.$$

Hydrastinine, $C_{11}H_{13}NO_3$.—This derivative crystallizes from ligroin in needles melting at 116–117°; it is readily soluble in organic solvents, little so, however, in water. Hydrastinine possesses an alkaline reaction and is without effect on polarized light. Physiologically it acts as a styptic.

Hydrastinine possesses a methyl group attached to the nitrogen,[9] but no methoxyl group (method of Zeisel); it is a secondary base forming benzoyl and acetyl derivatives; it contains an aldehyde group and may accordingly be converted into an oxime.

Its salts, like those of cotarnine, are formed with the elimination of a molecule of water:

$$\underset{\text{Hydrastinine}}{C_{11}H_{13}NO_3} + HCl \rightarrow \underset{\text{Hydrastinine hydrochloride}}{C_{11}H_{12}NO_2Cl} + H_2O.$$

Oxidation with nitric acid converts hydrastinine into apophyllenic acid. With potassium permanganate there is first obtained *oxyhydrastinine*, $C_{11}H_{11}NO_3$ (a weak base, melting-point 97–98°), then *hydrastinic acid*, $C_{11}H_9NO_6$.

On reduction with sodium amalgam, with zinc and hydrochloric acid, or by electrolysis, hydrastinine yields *hydrohydrastinine*, $C_{11}H_{13}NO_2$; this is a tertiary base, melts at 66°, and on oxidation is reconverted into hydrastinine.

When hydrastinine is heated with caustic potash it is decomposed into a mixture of oxyhydrastinine and hydrohydrastinine.

These reactions find their interpretation in the following formulæ:

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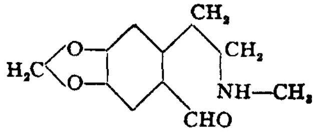
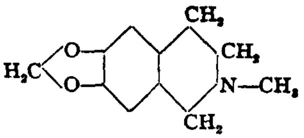
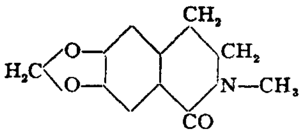
[9] Herzig and Meyer, M. 18, 379.



Hydrastinine



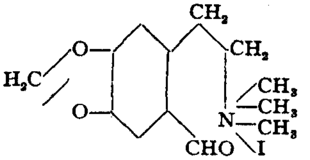
Hydrohydrastinine



Oxyhydrastinine

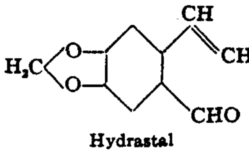
These formulæ find full confirmation through the following investigations of Freund.

Hydrastinine as a secondary base unites with two molecules of methyl iodide to form the methyl iodide of methylhydrastinine:



Methyl iodide of methylhydrastinine

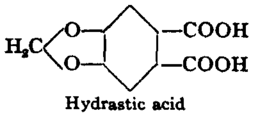
When this is heated with potassium hydroxide, it is decomposed into trimethylamine and a neutral, nitrogen-free substance, *hydrastal.* Hydrastal possesses the properties of an aldehyde and crystallizes in plates which melt at 78–79°:



Hydrastal

Hydrastal is readily oxidized by potassium permanganate, being thereby converted into a dibasic acid, *hydrastic acid,* $C_9H_6O_6$. This acid is also formed by the action of nitric or chromic acid on hydrastinic acid, the oxidation-product of hydrastinine.

From the following considerations, hydrastic acid is shown to be the methylene ether of 4,5-dioxyphthalic acid:

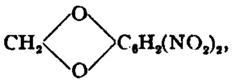


Hydrastic acid

1. When hydrastic acid is heated to 175° it is converted into its anhydride; with ammonia it yields an imide: the two carboxyls are consequently in the *ortho*-position.

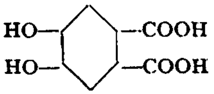
2. Fusion with caustic potash gives rise to protocatechuic acid and pyrocatechin.

3. Fuming nitric acid converts hydrastic acid into the methylene ether of dinitropyrocatechin,



a compound which was also obtained by Hesse and Jobst [10] from piperonylic acid by the same treatment (page 144).

4. By the successive action of phosphorus pentachloride and boiling water on hydrastic acid there is formed *normetahemipinic acid*,



This derivative was also prepared by Rossin [11] by treating metahemipinic acid (page 288) with hydriodic acid.

5. If hydrastic acid is heated to 160° either alone or with hydriodic acid there is formed this same normetahemipinic acid.

From all these reactions there naturally follows the constitu-

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[10] Hesse and Jobst, A. 199, 75.
[11] Rossin, M. 12, 486.

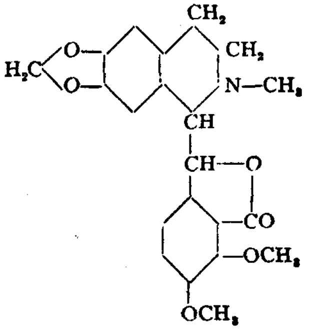
tion given above to hydrastic acid and from this constitution may be developed the formula already assigned to hydrastinine.

This constitution of hydrastinine and its derivatives finds a brilliant confirmation in the synthesis of hydrohydrastine, which was effected by Fritsch.[12] This synthesis has already been discussed (page 113).

Constitution of Hydrastine.—As we have already learned, hydrastine is decomposed by oxidation into opianic acid and hydrastinine. Since we now know the constitution of these two decomposition-products, it remains only to determine how they are united in hydrastine.

We proceed here as we did in the case of narcotine and note that the aldehyde group, which is common to both opianic acid and hydrastinine, does not appear in hydrastine; it is evident that the union is effected through the two CHO groups or the carbon atoms of these groups.

We develop, then, for hydrastine the following constitutional formula, which differs from that of narcotine only in the absence of a methoxyl group:



Hydrastine

2. BERBERINE.

Berberine is one of the few alkaloids that are found in a large number of plants. It was discovered in 1826 by Chevalier

[12] Fritsch, A. 286, 1.

and Pelletan[13] in the bark of the prickly-ash (*Xanthoxylum Clava-Herculis* L., family of the Rutaceæ) and described by them under the name of *xanthopicrite.* Büchner[14] in 1835 noted its occurrence in the root of the common barberry (*Berberis vulgaris* L.), in which it is the coloring principle and occurs to the extent of 1.3%. Perrins[15] obtained it also from the root of the golden seal (*Hydrastis canadensis* L.) (4%), and from that of *Coptis teeta* Wall. (family of the Ranunculaceæ) (8–9%). Eykman[16] found it together with nandinine in *Nandina domestica* Thumb. Other investigators have observed it in several plants belonging to the genera *Coscinium, Cœlocline, Cocculus, Orixa, Podophyllum, Geoffroya,* etc.

The empirical formula of berberine was for a long time in doubt, but this has now been established as $C_{20}H_{17}NO_4$. The alkaloid crystallizes in yellow prisms or needles containing a varying amount of water of crystallization (4–6 molecules). In the anhydrous condition it melts at 120°. With chloroform and acetone it forms crystalline derivatives, which may be used for its purification.

Berberine is little soluble in cold water, chloroform, and benzol; readily soluble in boiling water and in alcohol; insoluble in ether. It is a weak, tertiary base, somewhat poisonous, easily oxidized and without action on polarized light. Physiologically it acts as a nephritic.[17]

Its salts are yellow in color and possess a bitter taste.

Phosphorus pentachloride, hydroxylamine, and phenylhydrazine are without action on berberine; it consequently contains neither a hydroxyl nor an aldehyde or ketone group. There are two methoxyl groups in the molecule (Zeisel's method),[18] but there is no methyl attached to the nitrogen.[19]

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[13] Chevalier and Pelletan, *Journal de chimie médicale*, **2**, 314.
[14] Büchner, A. **24**, 228.
[15] Perrins, A. Suppl. **2**, 172.
[16] Eykman, R. **3**, 197.
[17] Mosse and Tautz, *Central-Blatt*, 1901, II, 786.
[18] Gaze, Schreiber, and Stubbe, A. Pharm. **228**, 604.
[19] Herzig and Meyer, M. **18**, 379.

Berberine is not attacked by dilute acids; it is also unaffected by alcoholic or aqueous potash.

According to Bernheimer[20] and Boedecker[21] fusion with caustic potash or distillation over lime or lead oxide converts berberine into a volatile base, which these investigators regarded as quinoline, but which was more probably isoquinoline.

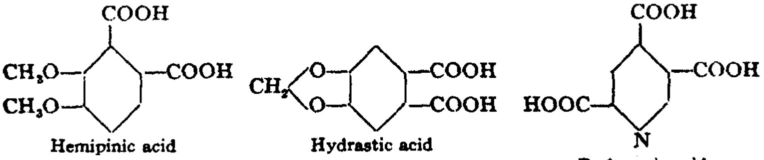
By the action of caustic potash on berberine, there are also formed, according to Hlasiwetz and Gilm,[22] two aromatic acids of the formulæ $C_8H_8O_4$ and $C_9H_8O_6$. Very little is known regarding the constitution of these acids. The first, *berberic acid*, has the composition and properties of a homopyrocatechin carboxylic acid.

Hlasiwetz and Gilm observed, furthermore, that berberine on reduction with zinc and sulphuric acid yields a tetrahydroderivative, *hydroberberine*, $C_{20}H_{21}NO_4$. This crystallizes from alcohol in needles which melt at 167°; it is a tertiary base and with weak oxidizing agents is reconverted into berberine.

The oxidation of berberine affords us a better insight into the constitution of the alkaloid. By the action of potassium permanganate in alkaline solution Schmidt[23] obtained two acids, *hemipinic* and *hydrastic acids*, which are also formed in the oxidation of hydrastine.

Further, by the action of concentrated nitric acid on berberine, Weidel[24] prepared berberonic acid, $\beta\gamma\alpha'$-pyridine tricarboxylic acid (page 71).

If we consider the formulæ of these three oxidation-products,



Hemipinic acid — Hydrastic acid — Berberonic acid

[20] Bernheimer, G. 13, 339.
[21] Boedecker, A. 66, 384; 69, 37.
[22] Hlasiwetz and Gilm, A. 115, 45; 122, 256; Suppl. 2, 191.
[23] Schmidt, B. 16, 2589; A. Pharm. 225, 141; 228, 596.
[24] Weidel, B. 12, 410.

we note that berberine, like hydrastine, contains three rings, a pyridine and two benzol rings. Of the latter, one possesses two methoxyl groups, the other the grouping CH_2O_2.

In what way now are these three rings united in the berberine molecule? This question has been answered by the investigations of Perkin, jun.[25]

He undertook anew the study of the action of permanganate on berberine and succeeded in isolating the following six oxidation-products in addition to the two acids described by Schmidt:

Oxyberberine	$C_{20}H_{17}NO_5$
Dioxyberberine	$C_{20}H_{17}NO_6$
Berberal	$C_{20}H_{17}NO_7$
Anhydroberberilic acid	$C_{20}H_{17}NO_8$
Berberilic acid	$C_{20}H_{19}NO_9$
Berilic acid	$C_{20}H_{15}NO_8$

Of these six derivatives berberilic acid and berberal have been particularly studied; we shall here consider only the latter and shall refer to the original articles in regard to the other members of the series.

Berberal, $C_{20}H_{17}NO_7$, crystallizes in plates which melt at 150°; it exhibits the properties of an aldehyde and is insoluble in alkalies in the cold.

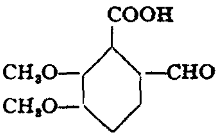
When boiled with dilute sulphuric acid it is decomposed into an acid and a nitrogenous derivative, according to the following equation:

$$\underset{\text{Berberal}}{C_{20}H_{17}NO_7} + H_2O \rightarrow C_{10}H_{10}O_5 + C_{10}H_9NO_3.$$

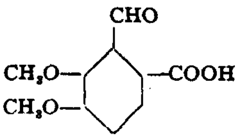
The body, $C_{10}H_{10}O_5$ (needles, melting-point 121–122°), is an isomer of opianic acid (page 305). Perkin accordingly named it *pseudo-opianic acid.* This acid is monobasic and contains an aldehyde group; its oxime, like that of opianic acid, on being heated yields hemipinimide. The isomerism of the two acids,

[25] Perkin, Soc. 55, 63; 57, 991.

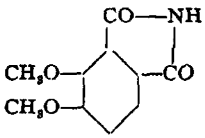
then, probably depends on the different positions of the groups CHO and COOH:



Opianic acid

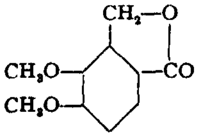


Pseudo-opianic acid

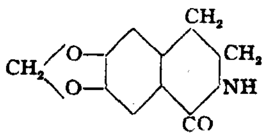


Hemipinimide

This view in regard to the constitution of pseudo-opianic acid is confirmed by its behavior on reduction with sodium amalgam; it is thereby converted into *pseudomeconine* (page 309):



The nitrogenous product, $C_{10}H_9NO_3$, resulting from the decomposition of berberine, crystallizes from hot water in plates which melt at 181–182°. In its properties it closely resembles oxyhydrastinine (page 317), from which it differs in composition by the absence of a CH_2 group. Perkin regarded it as *noroxyhydrastinine:*



In fact it may be converted into oxyhydrastinine in the following way: As a secondary base it forms a nitrosamine, and this

on being heated with caustic soda is decomposed into nitrogen and *ω-oxyethylpiperonylic acid:*

$$(CH_2O_2)C_6H_2\Big\langle\begin{array}{l} CO-N-NO \\ \qquad\quad | \\ CH_2-CH_2 \end{array} + NaOH \rightarrow$$

$$(CH_2O_2)C_6H_2\Big\langle\begin{array}{l} COONa \\ \\ CH_2-CH_2OH \end{array} + N_2.$$

If this latter derivative is now successively treated with phosphorus pentachloride and methyl alcohol it yields the methyl ester of *ω-chlorethylpiperonylic acid.*

When this ester is heated with a solution of methylamine to 130°,

$$(CH_2O_2)C_6H_2\Big\langle\begin{array}{l} COOCH_3 \\ \\ CH_2-CH_2Cl \end{array} + 2NH_2CH_3 \rightarrow$$

$$CH_3NH_2\cdot HCl + (CH_2O_2)C_6H_2\Big\langle\begin{array}{l} COOCH_3 \\ \\ CH_2-CH_2-NHCH_3 \end{array}$$

and the product thus obtained is treated with alcoholic potash, alcohol is split off and oxyhydrastinine is formed:

$$(CH_2O_2)C_6H_2\Big\langle\begin{array}{l} COOCH_3 \\ \\ CH_2-CH_2-NHCH_3 \end{array} \rightarrow$$

Methyl ester of ω-methylamido-ethylpiperonylic acid

$$(CH_2O_2)C_6H_2\Big\langle\begin{array}{l} CO-NCH_3 \\ \qquad\quad | \\ CH_2-CH_2 \end{array} + CH_3OH.$$

Oxyhydrastinine

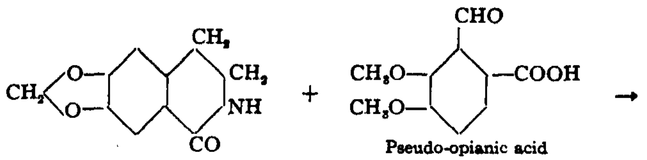
We saw above that berberal may take up a molecule of water and suffer decomposition into pseudo-opianic acid and noroxy-

hydrastinine. This reaction is reversible and berberal may accordingly be synthesized from pseudo-opianic acid and noroxyhydrastinine by the elimination of water:

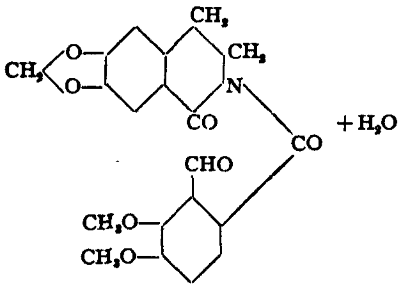
$$C_{10}H_{10}O_5 + C_{10}H_9NO_3 \rightleftarrows C_{20}H_{17}NO_7 + H_2O.$$

Pseudo-opianic acid Noroxyhydrastinine Berberal

Now, since the aldehyde group of pseudo-opianic acid is still present in berberal, the union has evidently been effected through the carboxyl group. On the other hand, it is most probable that, from the molecule of noroxyhydrastinine, it is the imide hydrogen atom which has been eliminated. The formation of berberal may then be represented as follows:

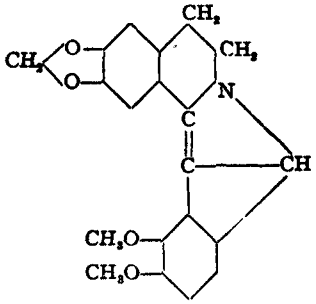


Noroxyhydrastinine Pseudo-opianic acid



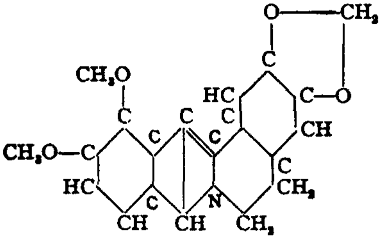
Berberal

The constitution of berberal being thus fixed, that of berberine, which contains three atoms less of oxygen, follows naturally, and we may with Perkin represent the constitution of the alkaloid by the following formula, which bears a close analogy to those of papaverine, narcotine, and hydrastine:

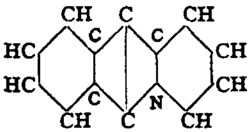


Berberine

Somewhat differently arranged, the berberine formula may be expressed as follows:



There appears here the atomic grouping



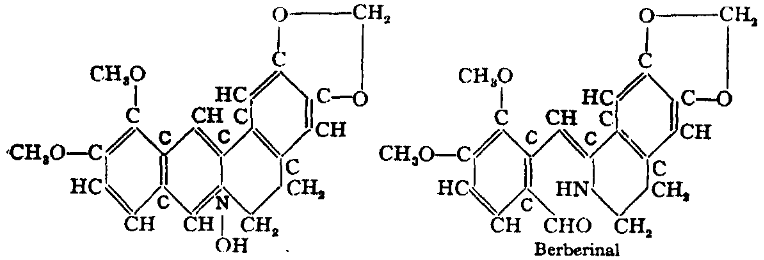
which Perkin regards as the chromophore group of berberine.

According to this formula of Perkin, the berberine molecule contains an asymmetric carbon atom. The alkaloid is, however, optically inactive. Gadamer[26] suggests that the free berberine is probably a quaternary base and is to be given the formula $C_{20}H_{18}NO_4\cdot OH$. The strongly alkaline, reddish-brown solution resulting from the decomposition of berberine acid sulphate

[26] Gadamer, A. Pharm. 239, 648; *Chemische Zeitung*, 26, 291, 385.

with barium hydroxide is supposed to contain this base, which he names ***berberinium hydroxide.*** If this solution is treated with excess of caustic soda, another modification of berberine is obtained, which is insoluble in water, weakly alkaline and appears to possess the character of an aldehyde. Gadamer names this second modification ***berberinal.***

The relation between the two forms he expresses as follows:



Berberinium hydroxide Berberinal

Berberinal may be reconverted into the hydroxide by simply warming it with water.

3. Canadine.

This alkaloid, which is found in small quantity in the root of *Hydrastis canadensis*, was studied by Schmidt[27] in 1894. Its formula is $C_{20}H_{21}NO_4$. It crystallizes in needles which melt at 132.5°. It is a tertiary base, is optically active, and possesses two methoxyl groups. Its alcoholic solution is inactive toward litmus.

An alcoholic solution of iodine converts canadine into berberine according to the following equation:

$$\underset{\text{Canadine}}{C_{20}H_{21}NO_4} + 2I_2 \rightarrow \underset{\text{Berberine hydriodide}}{C_{20}H_{17}NO_4 \cdot HI} + 3HI.$$

Canadine is accordingly a ***tetrahydroberberine;*** it differs

[27] Schmidt, A. Pharm. 232, 136.

only in its optical activity from the hydroberberine which results from the direct reduction of berberine (page 322).

Gadamer [28] has succeeded in separating inactive hydroberberine into its active constituents. The lævo-modification proves to be identical with canadine.

4. Nandinine.

Nandinine was discovered in 1885 by Eykman [29] in the root of *Nandina domestica*, where it is found together with berberine. Its formula is $C_{19}H_{19}NO_4$; it is an amorphous base, insoluble in water, but readily soluble in organic solvents. It acts as a poison.

5. Oxyacanthine.

Oxyacanthine was first observed in 1836 by Polex [30] in the root of the common barberry. He gave to it the formula $C_{16}H_{23}NO_6$, and described it as an amorphous substance melting at 139°. It is soluble in alkalies, insoluble in water.

Hesse [31] later took up the study of the alkaloid and found that it occurs in the plant in two forms: one is amorphous and melts at 139°, as Polex had observed, the other crystallizes in prisms and melts at 210°. For both these modifications Hesse proposes the formula $C_{18}H_{19}NO_3$; they are dextrorotatory and dissolve with great difficulty in alkalies. Potassium or barium hydroxide converts oxyacanthine into a new, isomeric base, *β-oxyacanthine*, which is characterized by its greater solubility in alkalies; it also occurs in two forms, of which one is amorphous (melting-point 150°), the other crystalline (melting-point 213-214°).

Oxyacanthine has also been observed in other species of

[28] Gadamer, A. Pharm. 239, 648.
[29] Eykman, R. 3, 196.
[30] Polex, A. Pharm. [2] 6, 271.
[31] Hesse, B. 19, 3190.

the genus *Berberis*. Rüdel[32] and Pommerehne[33] assign it the formula $C_{19}H_{21}NO_3$, and the latter investigator states that it contains a hydroxyl (benzoyl derivative) and one or two methoxyl groups.

6. Berbamine.

This alkaloid was isolated by Hesse from the root of the common barberry and received from him the formula $C_{18}H_{19}NO_3$. It crystallizes in leaflets containing two molecules of water of crystallization. The anhydrous alkaloid melts at 156°.

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[32] Rüdel, A. Pharm. **229**, 631.
[33] Pommerehne, A. Pharm. **233**, 127.

CHAPTER XXVI.

ALKALOIDS FROM CORYDALIS CAVA.

THE root of *Corydalis cava*, Schwgg. (family of the Fumariaceæ), contains the following eight alkaloids:

1.	Corydaline....................	$C_{22}H_{27}NO_4$
2.	Corybulbine....................	$C_{21}H_{25}NO_4$
3.	Isocorybulbine....................	$C_{21}H_{25}NO_4$
4.	Bulbocapnine....................	$C_{19}H_{19}NO_4$
5.	Corytuberine....................	$C_{19}H_{25}NO_4$
6.	Corycavine....................	$C_{23}H_{23}NO_6$
7.	Corycavamine	$C_{21}H_{21}NO_5$
8.	Corydine................probably	$C_{21}H_{23}NO_4$

Corydaline, the principal alkaloid of *Corydalis cava*, was discovered by Wackenroder[1] in 1826; its constitution, however, has been studied only within the last few years.

Corytuberine was isolated by Dobbie and Lauder[2] in 1893; *corybulbine*, *bulbocapnine*, and *corycavine* by Freund and Josephi[3] in 1892; *isocorybulbine* and *corycavamine* by Gadamer[4] in 1901.

In regard to the quantity of alkaloids found in the Corydalis, 10 kg. of roots yielded Ziegenbein[5] 57 gr. of corydaline, 41 gr. of bulbocapnine, 6 gr. of corycavine, and 4 gr. of corybulbine.

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[1] Wackenroder, *Berzelius Jahresbericht*, **7**, 220.

[2] Dobbie and Lauder, Soc. **61**, 244, 605; **62**, 485; **65**, 57; **67**, 17, 25; **71**, 657; **75**, 670; **79**, 87; **81**, 145, 157; **83**, 605. Proc. Soc. **15**, 129; **16**, 205; **17**, 252; **19**, 7.

[3] Freund and Josephi, B. **25**, 2411; A. **277**, 1.

[4] Gadamer, A. Pharm. **240**, 19, 81.

[5] Zeigenbein, A. Pharm. **234**, 492.

In the plant these alkaloids are in combination with malic and fumaric acids.

1. CORYDALINE.

Corydaline crystallizes from alcohol in prisms which melt at 134–135°. It is insoluble in water and alkalies, somewhat soluble in alcohol, readily soluble in ether, chloroform, and benzol. Its solutions possess a bitter taste and an alkaline reaction; they turn the plane of polarized light to the right. It is a tertiary base, but there is no methyl group attached to the nitrogen atom. It contains four methoxyl groups. When the alkaloid is heated with hydriodic acid, these are eliminated and there is formed a new, amorphous base, *corydaloline*, $C_8H_{15}N(OH)_4$.

An alcoholic solution of iodine oxidizes corydaline to a derivative, *dehydrocorydaline:*

$$\underset{\text{Corydaline}}{C_{22}H_{27}NO_4} + 2I_2 \rightarrow \underset{\text{Dehydrocorydaline hydriodide}}{C_{22}H_{23}NO_4 \cdot HI} + 3HI.$$

Dehydrocorydaline closely resembles berberine; like the latter alkaloid it forms yellow-colored salts; with acetone and chloroform it yields crystalline derivatives. Further, just as berberine on reduction is converted into a tetrahydro-derivative, inactive canadine (page 328), so dehydrocorydaline by the action of zinc and sulphuric acid yields inactive corydaline (melting-point 134–135°). It has as yet been found impossible to separate this inactive form into active components.[6] In some cases in the above reduction Gadamer[7] succeeded apparently in obtaining small quantities of a second inactive corydaline (melting-point 158–159°). This last he claims to have separated into its optically active constituents.

Possibly the inactivity of the form melting at 134–135° is due to intramolecular compensation, as in the case of mesotartaric acid.

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[6] Martindale, A. Pharm. 236, 214.
[7] Gadamer, A. Pharm. 240, 19.

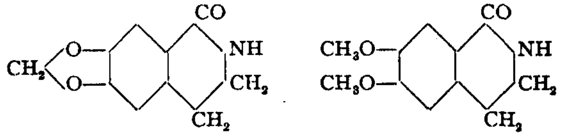
The close relation of corydaline to berberine is shown in its oxidation-products.

When corydaline is oxidized with potassium permanganate, there are formed, among other products, hemipinic acid, metahemipinic acid, and a nitrogenous product, *corydaldine*, $C_{11}H_{13}NO_3$.

The formation here of hemipinic acid, as also of metahemipinic acid, points to the presence of two benzol rings in the alkaloid. It may be assumed further that the benzol nucleus of the metahemipinic acid was in corydaline part of an isoquinoline ring, since metahemipinic acid is the ordinary oxidation-product of isoquinoline. Light has been thrown upon these inferences from a study of the nitrogenous product, corydaldine.

Corydaldine is a neutral body which melts at 175°; it does not react with phenylhydrazine; it contains two methoxyl groups, but no methyl attached to the nitrogen.[8] Its nitrogen atom is secondary in character. The formula of corydaldine may accordingly be represented as $C_9H_6O(NH)(OCH_3)_2$.

In all its behavior corydaldine bears a close resemblance to noroxyhydrastinine, $C_{10}H_7NO_3$ (page 324), and in its composition differs from the latter only in the carbon and hydrogen content CH_4. Since further noroxyhydrastinine possesses no methoxyl group, while corydaldine contains two, it seems not improbable that the latter differs from the former by the presence of two methoxyl groups in place of the dioxymethylene group:

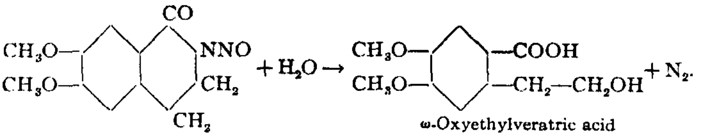


Noroxyhydrastinine   Corydaldine

Corydaldine like noroxyhydrastinine forms a nitroso-derivative. This derivative with sodium hydroxide loses nitrogen and experiences a change like that which occurs in the case of the

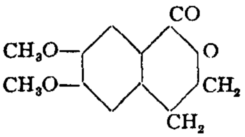
[8] Herzig and Meyer, M. 18, 385.

nitroso-derivative of noroxyhydrastinine under the same treatment (page 324):



Nitrosocorydaldine ω-Oxyethylveratric acid

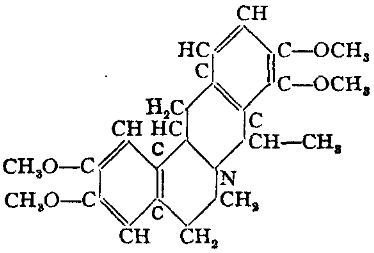
This hypothetical acid, however, is immediately converted by loss of water into *ω-oxyethylveratric anhydride:*



This anhydride melts at 138–139°, is little soluble in cold but readily soluble in hot water. It contains two methoxyl groups, and when heated with hydrochloric acid to 150° it is converted into a phenol derivative. Oxidation of the anhydride with potassium permanganate gives rise to metahemipinic acid.

As yet corydaline has not been synthesized from corydaldine.

Dobbie and Lauder offer provisionally the following formula for corydaline:



Corydaline

2. CORYBULBINE.

This alkaloid has been studied chiefly by Dobbie and Lauder and by Ziegenbein. Unlike corydaline, it is little soluble

in alcohol, almost insoluble in water and ether, but readily soluble in chloroform and benzol. Corybulbine is light yellow in color, melts at 238–239°, and is dextrorotatory.

The alkaloid closely resembles corydaline, and like the latter is a tertiary base. It differs from corydaline in that it possesses three methoxyl groups and readily dissolves in alkali.

Corybulbine is the lower homologue of corydaline, as is shown by its conversion into the latter on treatment with methyl iodide and potassium hydroxide:

Corydaline................ $C_{18}H_{15}N(OCH_3)_4$
Corybulbine.............. $C_{18}H_{15}N(OCH_3)_3(OH)$

3. Isocorybulbine.

Isocorybulbine crystallizes in leaflets which melt at 179–180°. It contains three methoxyl groups. It closely resembles corybulbine in optical activity, the specific rotation of the two bases being almost identical.

4. Bulbocapnine.

Recrystallized from alcohol or chloroform, bulbocapnine, $C_{19}H_{19}NO_4$, melts at 199°. It dissolves readily in all solvents except water; it is dextrorotatory.

Its solution in alkalies is green in color. It is a tertiary base which contains a nitrogen-methyl group.[9] Iodine is without action on the alkaloid. On treatment with acetic anhydride, there is formed a triacetyl derivative; bulbocapnine accordingly contains three hydroxyls. In addition to these there is a methoxyl group, so that the formula may be resolved into $C_{18}H_{13}N(OH)_3(OCH_3)$.

5. Corytuberine.

Corytuberine melts at 240°; it is soluble in alkalies and contains two methoxyl groups; it is optically active.

[9] Herzig and Meyer, M. 18, 386.

6. CORYCAVINE.

Corycavine, $C_{23}H_{23}NO_6$, forms needles or plates which melt at 216–217°; it is insoluble in water and alkalies and but little soluble in alcohol and ether. It is a strong, tertiary base. The alkaloid contains no methoxyl group and is not oxidized by iodine.

7. CORYCAVAMINE.

This base crystallizes in rhombic prisms melting at 149°. It is optically active; treatment with acetic anhydride renders it optically inactive. The *i-corycavamine* melts at 216–217°.

8. CORYDINE.

Corydine crystallizes from absolute ether. It melts at 129–130°. Its salts are difficultly soluble in water.

CHAPTER XXVII.

THE CINCHONA ALKALOIDS.

THE barks of several trees which belong to the genera *Cinchona* and *Remijia* (family of the Rubiaceæ) have been employed in Europe as a febrifuge since the middle of the seventeenth century. They contain a large number of alkaloids, all of which bear a close chemical relation to one another.

The habitat of the trees bearing the cinchona and allied barks is South America. In the latter half of the last century, however, these trees had become almost exterminated and an attempt was made to transplant them to India. This experiment has proved most successful.

The generic name Cinchona was given in honor of the countess of Chinchon, the vice-queen of Peru, who in 1638 is said to have been healed of a fever through the use of the bark. From this incident the curative properties of the different barks became generally known in Europe.

There are at present known twenty-one well-defined and characteristic cinchona alkaloids. These may be separated into six different groups according to the composition of the alkaloids and according to the nature of the decomposition-products which are produced by the action of mineral acids. Each of the first three groups contains a sub-group, which differs from the main group only in possessing a slightly greater amount of hydrogen.

Group 1..........$C_{19}H_{22}N_2O$, or $C_{19}H_{21}N_2(OH)$.

1. Cinchonine.
2. Cinchonidine.

Sub-group..........$C_{19}H_{24}N_2O$.

3. Cinchotine.

4. Cinchamidine.
5. Cinchonamine.

Group 2..........$C_{19}H_{22}N_2O_2$, or $C_{19}H_{20}N_2(OH)_2$.

6. Cupreïne.

Sub-group..........$C_{19}H_{24}N_2O_2$.

7. Quinamine.
8. Conquinamine.

Group 3..........$C_{20}H_{24}N_2O_2$, or $C_{19}H_{20}N_2(OH)(OCH_3)$.

9. Quinine.
10. Quinidine.

Sub-group..........$C_{20}H_{26}N_2O_2$.

11. Hydroquinine.
12. Hydroquinidine.

Group 4..........$C_{22}H_{26}N_2O_4$.

13. Chairamine.
14. Chairamidine.
15. Conchairamine.
16. Conchairamidine.

Group 5..........$C_{23}H_{26}N_2O_4$.

17. Aricine.
18. Cusconine.
19. Concusconine.

Group 6.

20. Homoquinine........$C_{39}H_{46}N_4O_4$.
21. Diconquinine........$C_{40}H_{46}N_4O_2$.

In addition to these alkaloids there is found in the cinchona-barks a large number of substances which do not contain nitrogen:

1. Acids (quinic, quinovic, quinotannic, quinovatannic, caffeïc, oxalic).

2. Neutral bodies (quinovine, quina-red, quinovic-red, cinchocerotine, cinchol, cupreol, cholestol, etc.).[1]

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[1] Thoms, A. Pharm. 235, 39.

1. Cinchonine.

Cinchonine was obtained in 1820 by Pelletier and Caventou [2] from gray quina. It is found in the bark of most of the *Cinchona* and *Remijia* species and is extracted from the mother-liquor in the preparation of quinine.

The formula first proposed for cinchonine was that of Laurent, $C_{19}H_{22}N_2O$. This was followed by the formula $C_{20}H_{24}N_2O$, which was advanced by Regnault. In 1879, however, Skraup [3] showed that the original formula, $C_{19}H_{22}N_2O$, was correct. This it is which is now accepted.

Cinchonine crystallizes from alcohol in anhydrous prisms which melt at 255°. In an atmosphere of hydrogen, or, better, *in vacuo*, it can be distilled without decomposition. It is almost insoluble in water and alkalies, little soluble in ether, chloroform, and benzol, somewhat more soluble in alcohol; its best solvent is a mixture of alcohol and chloroform.

It is a somewhat strong base, diacid and bitertiary. Its salt solutions do not fluoresce. Unlike quinine, it gives no color reaction with ammonia and chlorine. Both the free alkaloid and its salts are dextrorotatory. Its rotatory power has been employed quantitatively in determining the chinchonine in a mixture of cinchona alkaloids. Its physiological action is similar to that of quinine, but is less pronounced.

Cinchonine contains no methoxyl group; hydrochloric acid at 150° is without action. Its oxygen atom is in a hydroxyl group; Schützenberger [4] prepared a *monobenzoyl* and Hesse [5] a *monacetyl derivative.*

Isomeric Transformations of Cinchonine.—Various chemical reagents convert cinchonine into isomeric derivatives.

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[2] Pelletier and Caventou, A. ch. [2] 15, 291, 337.
[3] Skraup, A. 197, 353.
[4] Schützenberger, C. r. 47, 233.
[5] Hesse, A. 205, 321.

When cinchonine is heated for fifteen hours with an amyl alcohol solution of caustic alkali, a part of the alkaloid (about 5%) is transformed into the isomeric *cinchonidine*.[6]

Another isomer, *cinchonicine*, is formed by heating cinchonine with very dilute sulphuric acid at 130°.[7] This transformation to cinchonicine is effected still more easily if cinchonine sulphate or tartrate is heated. Cinchonicine has been studied chiefly by Hesse,[8] Howard,[9] Roques,[10] and by von Miller and Rohde.[11] It has been shown to be identical with *cinchotoxine* (page 353).

Cinchonidine and cinchonicine are, however, by no means the only isomers of cinchonine that are known. Indeed, nearly twenty isomers have been described which are obtained from cinchonine by the action of alkalies or of halogen acids or of sulphuric acid at different concentrations and at different temperatures.

Further, when cinchonine is heated with water to 140–160°, isomeric bases are formed; also under like treatment one isomer may be converted into another.

It is not our purpose to consider all these derivatives, which have been described under such names as *pseudo-cinchonine* (*cinchotine*), *tautocinchonine*, *α-* and *β-isocinchonine*, *apocinchonine* (*allocinchonine*), *cinchonigine*, *cinchoniline*, *homocinchonine*, *dicinchonine*, etc., and which have been studied by Hesse,[12] Skraup,[13] Comstock and Königs,[14] Jungfleisch and

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[6] Königs and Husmann, B. 29, 2185.

[7] Pasteur, C. r. 32, 110.

[8] Hesse, A. 166, 277; 178, 253.

[9] Howard, Soc. 25, 102.

[10] Roques, C. r. 120, 1170; A. ch. [7] 10, 234.

[11] von Miller and Rohde, B. 33, 3214.

[12] Hesse, A. 205, 330; 227, 153; 243, 131; 260, 213; 266, 245; 267, 142; 276, 88.

[13] Skraup, A. 201, 291; B. 25, 2909; M. 12, 431; 18, 411; 20, 571, 585; 21, 512; 22, 171, 253, 1083, 1097. Skraup and Zwerger, 21, 535; 23, 455. Zwerger, M. 24, 119.

[14] Comstock and Königs, B. 20, 2510.

Léger,[15] Pum,[16] Lippmann and Fleissner,[17] Löwenhaupt [18] and others.[19] The investigation of these isomers of cinchonine is far from complete. Above all, we are ignorant of the cause of this varied isomerism, although explanations have been attempted. It is not improbable that future study will decrease the number of these isomers by showing that some of them are identical with one another. The number of stereoisomers possible from the asymmetry of carbon atoms in the cinchonine molecule is not greater than eight.[20]

Addition-products of Cinchonine.—Cinchonine contains an ethylene group. By the action of chlorine or bromine in the cold addition-products are formed which contain two halogen atoms. The dichloride and dibromide are crystalline derivatives which are somewhat unstable and which behave as diacid bases.[21]

If cinchonine is treated in the cold with the halogen acids (concentrated solution) there are formed salts of new bases. These new bases are the addition-products of the alkaloid with the halogen acid and contain one molecule of hydrogen halide. The acid molecule may be eliminated by treatment with alkalies; cinchonine, however, is only regenerated in part, the chief product being a mixture of isomeric derivatives.

Cinchonine also adds hydrogen under the action of sodium amalgam or sodium and alcohol.[22] The derivatives thus formed (*dihydrocinchonine, tetrahydrocinchonine*) have been little studied; they appear to be secondary bases. None of them, however, is

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[15] Jungfleisch and Léger, C. r. **105**, 1255; **106**, 357, 657, 1410; **108**, 952; **112**, 942; **113**, 651; **114**, 1192; **117**, 42; **118**, 29, 536; **119**, 1268; **120**, 325; **132**, 410.

[16] Pum, M. **12**, 582; **13**, 676; **15**, 446.

[17] Lippmann and Fleissner, M. **12**, 661; **13**, 429; **14**, 371; B. **24**, 2827; **26**, 2005.

[18] Löwenhaupt, M. **19**, 461.

[19] von Arlt, M. **20**, 425. Langer, M. **22**, 151. Arpad von Pessics, M. **23**, 443.

[20] Skraup, B. **35**, 3981; **36**, 141.

[21] Laurent, C. r. **20**, 1586. Comstock and Königs, B. **17**, 1984; **19**, 2853; **20**, 2510; **25**, 1539.

[22] Zorn, J. pr. [2] **8**, 279. Skraup, B. **11**, 311. Koneck von Norwall, M. **16**, 321; B. **28**, 1637, 1843. Hesse, B. **28**, 1424.

identical with any of the natural alkaloids, cinchotine, cinchamidine, and cinchonamine.

Action of Alkalies on Cinchonine.—This action was one of the earliest studied in the field of alkaloidal chemistry. It was employed in 1842 by Gerhardt [23] in investigating the constitution of cinchonine, in 1855 by Williams,[24] and more recently by Butlerow,[25] Wischnegradsky,[26] Oechsner,[27] Hoogewerff and van Dorp.[28]

If cinchonine is distilled with caustic potash, there passes over first a quantity of *quinoline;* in the retort there remains a solid mass, which at a higher temperature is likewise decomposed, yielding *β-lutidine* (β-ethylpyridine), and leaving as residue a mixture of potassium acetate, propionate, and butyrate.

Quinoline and β-lutidine are, however, not the only volatile derivatives obtained in this distillation. Williams has shown that there are also formed lepidine (γ-methylquinoline), pyrrol, pyridine bases (pyridine, picoline, collidine), and an entire series of higher quinoline derivatives.

Oechsner isolated from these distillation-products a *lutidine*, a *collidine*, and a base, $C_9H_{11}N$ (probably *tetrahydroquinoline*). We may add further that, according to Wischnegradsky, when cinchonine is distilled over caustic potash and copper oxide, only quinoline is formed; that, according to Hoogewerff and van Dorp, distillation with lead oxide gives rise to lepidine alone; and finally that, according to Michael,[29] when cinchonine is heated with alcoholic potash, it gives a derivative, $C_{20}H_{26}N_2$, or $(C_{18}H_{21}N_2)(C_2H_5)$, which on fusion with caustic potash yields the same mixture of bases as does cinchonine itself under similar treatment.

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[23] Gerhardt, A. 42, 310; 44, 279.

[24] Williams, *Chemical News*, 44, 307 J. 1855, 550; 1864, 437.

[25] Butlerow, B. 11, 1253.

[26] Wischnegradsky, B. 12, 1480; 13, 2310.

[27] Oechsner, C. r. 91, 296; 92, 413; 94, 87; 95, 298; 96, 200, 437; 98, 235, 1438; 99, 1077; 100, 806.

[28] Hoogewerff and van Dorp, R. 2, 1.

[29] Michael, Am. Chem. Jour. 7, 183.

Distillation of cinchonine over zinc-dust converts the alkaloid into quinoline and a small quantity of picoline.[30]

Oxidation of Cinchonine.—1. Potassium permanganate in sulphuric acid solution acts upon cinchonine in the cold. An atom of carbon is split off as formic acid and the remainder of the molecule is oxidized to *cinchotenine:*

$$\underset{\text{Cinchonine}}{C_{19}H_{22}N_2O} + 4O \rightarrow \underset{\text{Cinchotenine}}{C_{18}H_{20}N_2O_3} + \underset{\text{Formic acid}}{CH_2O_2}.$$

Cinchotenine was first obtained by Caventou and Willm;[31] it has been studied by Skraup.[32] It crystallizes with three molecules of water in needles or leaflets; it is somewhat soluble in water, melts at 197–198°, and is dextrorotatory. It is neutral in reaction, dissolves in both alkalies and acids, and forms a bitertiary base.

Cinchotenine still contains the alcoholic hydroxyl of cinchonine, since it forms an acetyl derivative. Further, when benzoylcinchonine is oxidized with potassium permanganate it yields *benzoylcinchotenine,* which is decomposed by hydrolysis into benzoic acid and cinchotenine.

Cinchotenine possesses also a carboxyl group, since it is converted into an ester with alcohol and hydrogen chloride.

It forms no addition-product with hydriodic acid; it consequently, unlike cinchonine, contains no double bond. From this it is highly probable that the reaction which causes its formation depends on the conversion of a side-chain, $-CH{=}CH_2$, into a carboxyl group:

$$\underset{\text{Cinchonine}}{C_{17}H_{18}N_2(OH)(CH{=}CH_2)} \rightarrow \underset{\text{Cinchotenine}}{C_{17}H_{18}N_2(OH)(COOH)}$$

On more energetic oxidation cinchotenine yields the same derivatives as does cinchonine under like treatment.

[30] Fileti, G. 11, 20.
[31] Caventou and Willm, Bl. [2] 12, 214.
[32] Skraup, A. 197, 376; B. 28, 12; M. 16, 159.

2. By heating cinchonine sulphate with fourteen parts of dilute sulphuric acid for two days, Jungfleisch and Léger[33] obtained two oxidation-products of the formula $C_{19}H_{22}N_2O_2$, *α-oxycinchonine* and *β-oxycinchonine* (at the same time there are formed three isomers of cinchonine, *cinchonifine, cinchonigine,* and *cinchoniline*). α-Oxycinchonine crystallizes from alcohol in prisms which melt with decomposition at 252°; it is dextrorotatory and forms a diacetyl derivative; it accordingly contains two hydroxyl groups. β-Oxycinchonine crystallizes in needles which melt at 273°; it also yields a diacetyl derivative and is dextrorotatory.

3. When cinchonine dibromide (page 341) is treated with alcoholic potash, two molecules of hydrogen bromide are lost and a base is obtained which possesses two hydrogen atoms less than cinchonine and which Comstock and Königs[34] called *dehydrocinchonine:*

$$\underset{\text{Cinchonine dibromide}}{C_{19}N_{22}Br_2N_2O} + 2KOH \rightarrow \underset{\text{Dehydrocinchonine}}{C_{19}H_{20}N_2O} + 2KBr + 2H_2O.$$

This derivative melts at 202–203°; it probably contains an acetylene bond, —C≡C—, instead of the ethylene of cinchonine, since oxidation with potassium permanganate converts both bases into the above-mentioned cinchotenine.

4. When cinchonine is oxidized with chromic acid, the alkaloid is converted to the extent of about 50% into *cinchoninic acid* (γ-quinoline carboxylic acid, page 104).[35]

Cinchoninic acid is also formed by heating an acidified solution of cinchonine with potassium permanganate. There are obtained at the same time *α-carbocinchomeronic acid* and *cinchomeronic acid.*[36]

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[33] Jungfleisch and Léger, *loc. cit.*

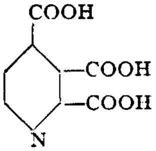
[34] Comstock and Königs, B. 19, 2853; 20, 2510; 25, 1539; 28, 1986.

[35] Königs, B. 12, 97. Skraup, B. 12, 230; A. 201, 291. Königs and Lossow, B. 32, 717.

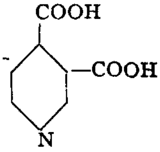
[36] Caventou and Willm, Bl. [2] 12, 214. Hesse, A. 176, 232. Dobbie and Ramsay, Soc. 35, 189.

From the oxidation of cinchonine with dilute nitric acid, Weidel[87] also secured the acids, *cinchoninic*, *α-carbocinchomeronic*, and *cinchomeronic*. In addition to these he found the bodies *quinolinic acid*, a *nitro-dioxyquinoline*, and a base of the formula $C_{16}H_{18}N_2O_5$.

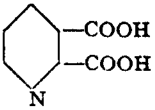
The constitution of three of these acids we have already discussed (pages 61, 62, 67):



α-Carbocinchomeronic acid

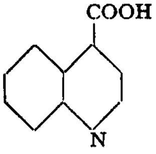


Cinchomeronic acid

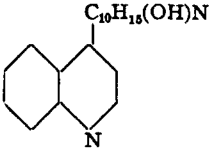


Quinolinic acid

Now these three acids result from the oxidation of cinchoninic acid; the latter alone is the product uniformly obtained from the action of all strong oxidizing agents on cinchonine. Hence it follows that cinchonine is a quinoline derivative, possessing in the γ-position a side-chain, which oxidation converts into a carboxyl group. This side-chain contains the hydroxyl of cinchonine; for, if it were in the quinoline nucleus, it would appear in the oxidation-product and there would result an oxycinchoninic acid instead of cinchoninic. We thus arrive at the following formulæ:



Cinchoninic acid



Cinchonine

5. As we saw above, when cinchonine is oxidized with chromic acid there is formed a quantity of cinchoninic acid which corresponds to about one-half of the weight of the alkaloid. The remainder of the reaction-product is a sirupy mass, which shows

[87] Weidel, A. 173, 76.

no tendency to crystallize. It evidently contains the oxidation-products of the group $C_{10}H_{15}(OH)N$. Many attempts have been made to obtain from it well-defined derivatives, which might afford some indication at least regarding the constitution of this so-called "second half" of the cinchonine molecule.

Weidel and Hazura [38] distilled 580 g. of the sirup over zinc-dust and obtained in the distillate a mixture of substances from which they were able to isolate 30 g. of quinoline, 35 g. of β-ethyl-pyridine, 1 g. of pyridine, and traces of pyrrol.

Comstock and Königs [39] derived from the sirup, on addition of bromine, two bromine derivatives of the formulæ $C_9H_{13}Br_2NO + \frac{1}{2}H_2O$ and $C_{10}H_8Br_3NO$. The latter of these is probably a *tribromoxylepidine.*

In his study of cinchonine, Skraup [40] obtained results somewhat more satisfactory; he succeeded in isolating from the sirupy mass the following four bodies:

1. *Kynurine* (γ-oxyquinoline, page 87).
2. *Cincholoipone*, a base of the formula $C_9H_{17}NO_2$.
3. *Cincholoiponic acid*, a dibasic acid, $C_8H_{13}NO_4$.
4. *Loiponic acid*, a dibasic acid, $C_7H_{11}NO_4$.

Of these derivatives only the two latter can be regarded as oxidation-products of the second half of the cinchonine molecule. It has been found on the one hand that kynurine is a decomposition-product of cinchoninic acid, a small quantity of which would easily remain in the sirup, and on the other hand that the formation of cincholoipone arises from the presence of a little cinchotine (hydrocinchonine), which is contained in commercial cinchonine. Pure cinchonine does not yield cincholoipone on oxidation.

Finally Königs [41] obtained from the sirup a derivative whose composition is $C_9H_{15}NO_2$, and which he named *meroquinene.*

Cincholoiponic acid, *loiponic acid*, and *meroquinene* are ac-

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[38] Weidel and Hazura, M. 3, 770; B. 16, 84.

[39] Comstock and Königs, B. 17, 1984.

[40] Skraup, M. 7, 517; 9, 783; 10, 39, 220; 16, 159; 17, 365; B. 28, 12.

[41] Königs, B. 27, 900, 1501; 28, 1986, 3143, 3148; 30, 1326, 1332. Königs and Höppner, B. 31, 2358.

cordingly the true oxidation-products of the atomic complex $C_{10}H_{16}NO$ of cinchonine. We shall now consider these substances more carefully.

Cincholoiponic Acid, $C_8H_{13}NO_4$, crystallizes from an aqueous solution in prisms which contain a molecule of water and which melt at 126–127°; the anhydrous acid melts at 225–226°. It is dextrorotatory; after five hours' heating with potassium hydroxide, however, it becomes lævorotatory.

It unites with both acids and bases. It is a secondary base (formation of a nitrosamine, acetyl and benzoyl derivatives) and a dibasic acid:

$$NH : C_6H_{10}(COOH)_2.$$

The two carboxyls probably stand in an *ortho*-position to each other, since heating the acid with resorcin and zinc chloride or sulphuric acid gives rise to a fluorésceïn formation.

Cincholoiponic acid is a saturated derivative of great stability; neither chromic acid nor sodium amalgam affect it and bromine and hydriodic acid act upon it only at a very high temperature.

When the hydrochloride of cincholoiponic acid is heated to 260–270° with dilute sulphuric acid, there are formed *γ-picoline* and two isomeric acids of the formula $C_7H_{13}NO_2$ (pipecoline monocarboxylic acid?).

Cincholoiponic acid accordingly appears to be a *γ-pipecoline dicarboxylic acid.*

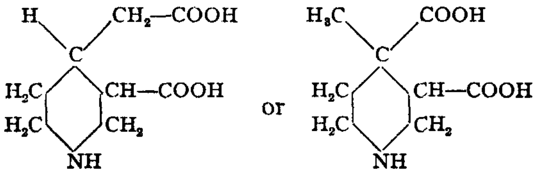
By the action of potassium permanganate in alkaline solution cincholoiponic acid is converted into its lower homologue, loiponic acid:

$$\underset{\text{Cincholoiponic acid}}{C_8H_{13}NO_4} + 3O \rightarrow \underset{\text{Loiponic acid}}{C_7H_{11}NO_4} + CO_2 + H_2O.$$

Loiponic Acid, $C_7H_{11}NO_4$, crystallizes from water in prisms which melt with decomposition at 259–260°. It is dibasic and contains a NH group (acetyl derivative). From its composition and properties loiponic acid appears to be a pyridine dicarboxylic acid and this view is confirmed by the experiments of Königs. Loiponic acid is steroisomeric with hexahydrocinchomeronic acid (page 64); by the action of potassium hydroxide both acids

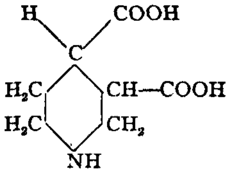
are readily converted into the same derivative. The new acid crystallizes from water, in which it is somewhat difficultly soluble in the cold, and melts at 275°.

From these data cincholoiponic and loiponic acids may be represented by the following formulæ:



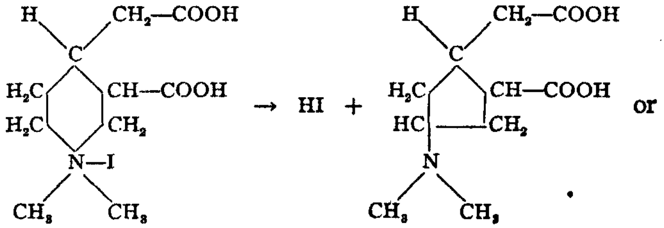
Cincholoiponic acid

I II



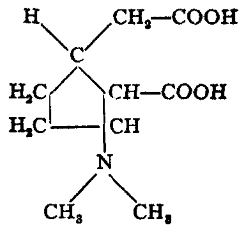
Loiponic acid
(Hexahydrocinchomeronic acid)

Of the two formulæ for cincholoiponic acid, Skraup[42] has shown that the first is probably correct. By the action of caustic potash on the methyl iodide of *methylcincholoiponic ester*, he obtained an acid whose general properties led him to regard it as a pentamethylene derivative. The reaction he represents as follows:

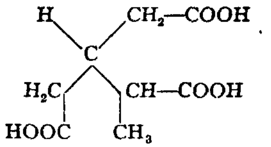


Methyl iodide of methylcincholoiponic acid

[42] Skraup, M. 21, 879.



Fused with potassium hydroxide, the new derivative is decomposed into dimethylamine and a tribasic acid, whose constitution as he showed later by a synthesis of the acid is expressed by the formula



It is difficult to see how an acid of this constitution could be formed here if the constitution of cincholoiponic acid is represented by formula II.

Meroquinene, $C_9H_{15}NO_2$, crystallizes from methyl alcohol in needles which melt at 222°; it is dextrorotatory; in its action toward litmus it is neutral. It yields a nitrosamine and an acetyl derivative; it is consequently a secondary base. It is, however, at the same time a pronounced acid; it possesses a carboxyl group, since warming it with alcohol and hydrochloric acid converts it into an ester, also by the action of hydrochloric or hydrobromic acid the carboxyl group may be eliminated.

On distillation with zinc-dust it yields a pyridine base, probably *β-lutidine.*

On heating meroquinene with hydrochloric acid to 240° with or without the addition of mercuric chloride, Königs obtained a base of the formula $C_8H_{11}N$, which he regarded as identical with β-collidine (γ-methyl-β-ethylpyridine, page 42). Oxidation converts this base into *homonicotinic acid* (γ-methyl-β-pyridine carboxylic acid) and *cinchomeronic acid.*

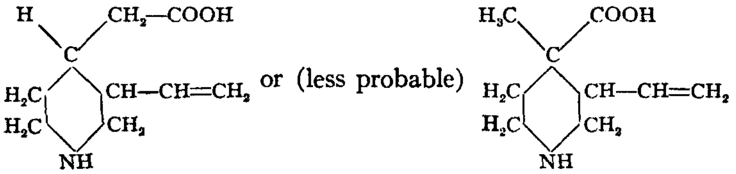
From its composition and from these different reactions it follows that meroquinene is a derivative of a reduced pyridine ring; that in the γ-position of this ring there is a methyl group and in the β-position a chain of two carbon atoms; and that, furthermore, the base possesses a carboxyl group.

By the oxidation of meroquinene with potassium permanganate, cincholoiponic and formic acids are produced:

$$\underset{\text{Meroquinene}}{C_9H_{15}NO_2} + 4O \rightarrow \underset{\text{Cincholoiponic acid}}{C_8H_{13}NO_4} + \underset{\text{Formic acid}}{CH_2O_2}.$$

This reaction recalls the transformation of cinchonine into cinchotenine (page 343), whereby a $CH_2{=}CH_2$ group is converted into formic acid and a carboxyl group.

All these facts point concordantly to the following formula for meroquinene:



Meroquinene

Thus the formulæ of cincholoiponic acid, loiponic acid, and meroquinene appear to be fairly well established.

It is noteworthy that in all three substances the imide group NH occurs, while cinchonine itself is a bitertiary base. It is impossible to consider here that a change has been brought about similar to that in which tropine is transformed into tropigenine and in which a nitrogen-alkyl is eliminated, since cinchonine contains no such group. Farther on we shall note an explanation which has been proposed by Miller and Rohde to account for the above.

Briefly to summarize, the data contributing to our knowledge of the constitution of cinchonine from a study of the oxidation-products of the alkaloid are as follows:

The molecule of cinchonine contains a quinoline and a piperidine nucleus. The two nuclei are united by a chain of two or three carbon atoms, which is attached on the one side to the γ-carbon atom of the quinoline, on the other to the γ-carbon atom of the piperidine. On oxidation this chain is ruptured and from it result two carboxyl groups, one of which is found in the cinchoninic acid, the other in the meroquinene. In this chain also must lie the alcoholic hydroxyl of cinchonine, since this does not occur in either of the two oxidation-products considered.

Quaternary Derivatives of Cinchonine.—As a bitertiary base, cinchonine can form addition-products with two molecules of an alkyl halide. If, however, the action takes place at the ordinary temperature, monoalkyl derivatives result, while the dialkylated bodies are formed only at a higher temperature (150°). These quaternary derivatives have been studied by Stahlschmidt [43] and by Claus and his students.[44]

Since the two nitrogen atoms in the cinchonine molecule occupy relatively different positions, it is evident that the monoalkyl derivatives should exist in two isomeric forms, according as the alkyl halide is attached to one or the other nitrogen atom. Skraup and Konek von Norwall [45] have indeed succeeded in preparing two isomeric monoethyl derivatives. If cinchonine and ethyl iodide are brought together directly, a different derivative is obtained than what is formed when the monohydriodide of the alkaloid is heated with ethyl iodide in excess. In the latter case there is formed a salt, $C_{19}H_{22}N_2O \cdot HI \cdot C_2H_5I$, which ammonia or sodium carbonate converts into the ethyl iodide $C_{19}H_{22}N_2O \cdot C_2H_5I$ (yellow crystals, melting at 184°). This differs from the derivative directly obtained by Claus, which is colorless and melts at 259–260°.

The former, *isocinchonine ethiodide*, necessarily has the alkyl attached to that nitrogen atom which is less strongly

[43] Stahlschmidt, A. 90, 218.

[44] Claus and Kemperdick, B. 13, 2286. Claus and Müller, B. 13, 2290. Claus and Treupel, B. 13, 2294.

[45] Skraup and Konek von Norwall, B. 26, 1968; M. 15, 37.

basic. On oxidizing the iso-derivative with potassium permanganate, Skraup [46] obtained the ethyl iodide of cinchoninic acid. From this it follows that the nitrogen of the quinoline nucleus is less basic than the other and that in the mono-salts of cinchonine as in its monoalkyl halide derivatives directly prepared, the acid, or the alkyl halide, is attached to the nitrogen of the "second half."

The monoalkyl derivatives produced by the direct action of the alkyl halides are decomposed by alkalies.[47] There are thus formed the *alkylcinchonines*, bases diacid and bitertiary, like cinchonine itself:

$$(C_{19}H_{22}NO)\equiv N\begin{matrix} \diagup CH_3 \\ \diagdown I \end{matrix} + KOH \rightarrow$$

Monomethyl iodide of cinchonine

$$(C_{19}H_{21}NO)=N-CH_3 + H_2O + KI.$$

Methylcinchonine

Methylcinchonine crystallizes from ether or acetone in plates which melt at 74–75°. On this derivative Freund and Rosenstein [48] employed Hofmann's process of exhaustive methylation. They prepared first the monomethyl iodide, heated this with caustic potash and obtained thereby an oily base of the composition of a *dimethylcinchonine:*

$$(C_{19}H_{21}NO)=N\begin{matrix} \diagup CH_3 \\ -CH_3 \\ \diagdown I \end{matrix} + KOH \rightarrow$$

Monomethyl iodide of methyl cinchonine

$$(C_{19}H_{20}NO)-N\begin{matrix} \diagup CH_3 \\ \diagdown CH_3 \end{matrix} + H_2O + KI.$$

Dimethylcinchonine

This, in turn, can now add a second molecule of methyl iodide. When the addition-product thus obtained is treated with

[46] Skraup, M. 15, 433.
[47] Claus and Müller, B. 13, 2290.
[48] Freund and Rosenstein, B. 25, 880; A. 277, 277.

alkali, the molecule is decomposed into trimethylamine and a body of weakly basic properties which contains only one atom of nitrogen. The study of this body has not been further pursued.

Freund and Rosenstein have shown by oxidation of the different derivatives that the three methyl groups introduced are all attached to the nitrogen of the " second half"; they obtained uniformly only cinchoninic acid.

From this behavior it follows that there is no methyl group attached to the nitrogen of the second half of the cinchonine molecule, since, as is indicated above, the formation of trimethylamine occurs only after the successive introduction of three methyl groups.

Cinchotoxine.—In 1894 von Miller and Rohde[49] made the observation that methylcinchonine yields with phenylhydrazine a hydrazone, while cinchonine itself did not give this reaction. In the formation of methylcinchonine, then, it would seem to be necessary to assume that the transformation was accompanied by a molecular rearrangement, the hydroxyl group being converted into a carbonyl.

Von Miller and Rohde consequently continued their study of the action of phenylhydrazine on cinchonine. They found that prolonged heating at 100° of a mixture of these two substances in a solution of dilute acetic acid gave rise also to a hydrazone. A molecular rearrangement of cinchonine was thus effected apparently by the action of the acetic acid. The experiment was repeated without the addition of the phenylhydrazine and there resulted in fact a new base isomeric with cinchonine. This new base is highly poisonous and on that account has received the name of *cinchotoxine.*

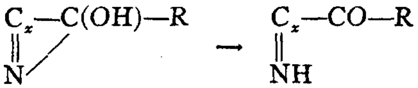
Cinchotoxine crystallizes with some difficulty from ether; it melts at 58–59° and dissolves easily in the ordinary organic solvents with the exception of ligroin; in water it is soluble only with difficulty. It is a strong base, which expells ammonia from its salts and unites readily with carbonic acid. Cinchotoxine is identical with cinchonicine (page 340).

[49] von Miller and Rohde, B. 27, 1187, 1279; 28, 1056.

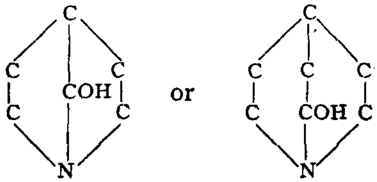
One nitrogen atom in cinchotoxine is tertiary, the other secondary (formation of a nitrosamine); treated with methyl iodide, the base adds one molecule and forms the hydriodide of methylcinchonine of Claus and Müller (page 351). From this it follows that the latter, as its reaction with phenylhydrazine would also lead us to infer, is not a derivative of cinchonine, but is a methylcinchotoxine.

Cinchotoxine forms a hydrazone and an oxime. It is consequently either an aldehyde or a ketone. We must, however, decide in favor of the latter alternative, since methylcinchotoxine on oxidation with silver oxide does not yield an acid and its oxime cannot be converted into a nitrile by dehydration.

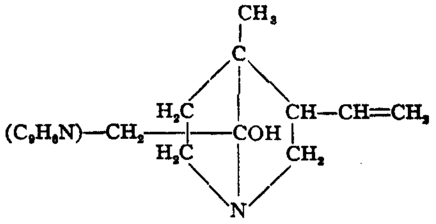
The transformation of cinchonine (a tertiary base with an alcoholic group) into cinchotoxine (a secondary base with a ketone grouping) may be explained by the following molecular change:



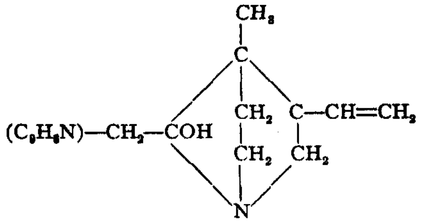
This result is of the highest importance in the study of the constitution of cinchonine. It shows, indeed, that the carbon atom to which the hydroxyl is attached is directly united with the nitrogen atom of the "second half." Now, we have already shown that this hydroxyl forms a part of a side-chain which is bound to the γ-carbon atom of the piperidine ring. In the second half of the cinchonine molecule we must, consequently, assume the existence of the grouping



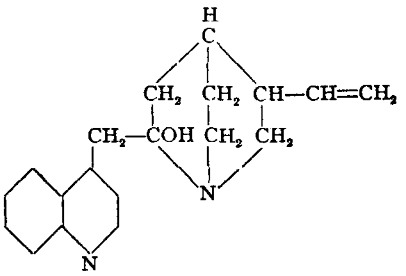
In accordance with this view, as also in accordance with the results obtained from the oxidation of cinchonine (page 343), von Miller and Rohde propose the following constitution for the alkaloid:



This may also be formulated as

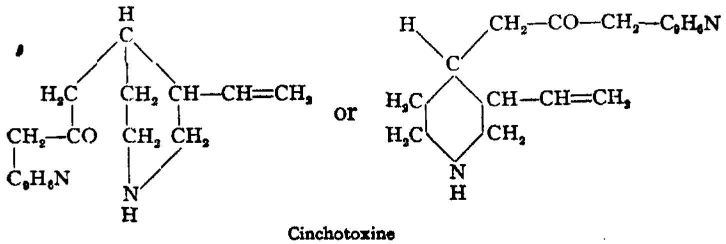


For reasons which will be developed further on we believe that the following formula (which was also considered by von Miller and Rohde) is to be preferred to the above:



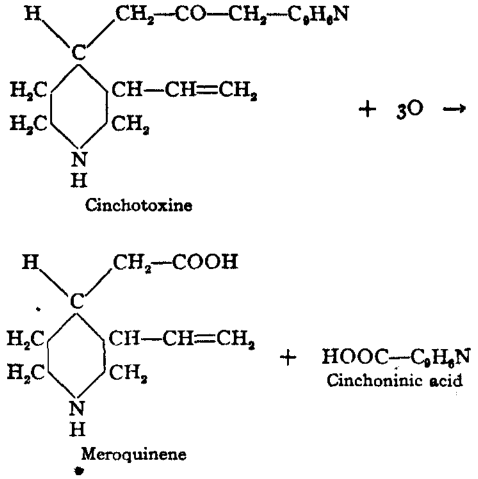
Cinchonine

Cinchotoxine has then the following constitution:



Cinchotoxine

These formulæ explain in a satisfactory way the fact that tertiary cinchonine on oxidation yields derivatives which have the character of secondary bases, such as meroquinene, cincholoiponic acid, and loiponic acid. In the action of chromic acid on cinchonine we may consequently assume that there is first formed cinchotoxine, which is then decomposed into cinchoninic acid and meroquinene:



Cinchene.—Königs and his students[50] have published since 1880 a long series of investigations whose chief purpose has been to solve the question concerning the constitution of the "second half" of cinchonine.

As starting material they chose *cinchonine chloride*, $C_{19}H_{21}ClN_2$, which is formed by the action of a mixture of phosphorus pentachloride and oxychloride on cinchonine hydrochloride. This body is

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[50] Comstock and Königs, B. **13**, 286; **14**, 103, 1852; **17**, 1984; **18**, 1219, 2379; **19**, 2853; **20**, 2510, 2674; **25**, 1539. Königs and Nef, B. **20**, 622. Königs and Heymann, B. **21**, 1424. Königs, B. **23**, 2669, 3144; **26**, 713; **27**, 900; **28**, 3143; **34**, 4322, 4336; **35**, 1349. Königs and Höppner, B. **31**, 2355. Königs and Bischkopff, B. **34**, 4327. Königs and Stockhausen, B. **34**, 4330; **35**, 2554. Königs and Hoppe, B. **35**, 1343. Königs and Schönewald, B. **35**, 2980.

derived from cinchonine by substituting a chlorine atom for the hydroxyl group:

$$\underset{\text{Cinchonine}}{C_{19}H_{21}N_2(OH)} \qquad \underset{\text{Cinchonine chloride}}{C_{19}H_{21}N_2Cl}$$

Cinchonine chloride is dextrorotatory and crystallizes in prisms which melt at 72°.

On reducing it with iron and dilute sulphuric acid, Königs obtained a *desoxycinchonine*, $C_{19}H_{22}N_2$, melting at 90–92°; this is also dextrorotatory.

On treatment with alcoholic potash, cinchonine chloride loses a molecule of hydrogen chloride according to the equation:

$$C_{19}H_{21}N_2Cl + KOH \rightarrow C_{19}H_{20}N_2 + KCl + H_2O.$$

The body, $C_{19}H_{20}N_2$, which may be viewed as derived from cinchonine by the loss of a molecule of water, was named *cinchene* by Königs. It crystallizes from ether or ligroin in leaflets which melt at 123–125°.

Cinchene is dextrorotatory; the optical activity of cinchonine accordingly does not depend alone on the asymmetry of that carbon atom with which the hydroxyl is united, but there must be still other asymmetric carbon atoms in the cinchonine molecule. This possibility finds expression in the formula for the alkaloid given above.

Cinchene, like cinchonine, is a bitertiary base; oxidation with chromic acid converts it into cinchoninic acid.

Cinchene is an unsaturated derivative. One would suppose that it ought to have two double bonds, since cinchonine possesses one; it adds, however, only one molecule of hydrogen bromide or two atoms of bromine.

When cinchene dibromide is treated with alcoholic potash, two molecules of hydrogen bromide are eliminated and *dehydrocinchene* is formed:

$$\underset{\text{Cinchene dibromide}}{C_{19}H_{20}N_2Br_2} \rightarrow \underset{\text{Dehydrocinchene}}{C_{19}H_{18}N_2} + 2HBr.$$

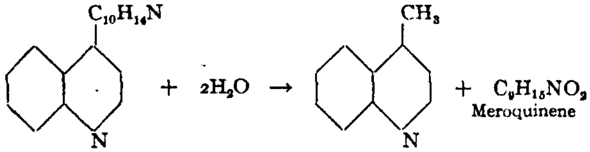
This derivative may also be obtained from dehydrocinchonine (page 344), if the latter is successively treated with phosphorus pentachloride and alcoholic potash.

Dehydrocinchene crystallizes from dilute alcohol in needles containing apparently three molecules of water of crystallization; it melts near 60°; the anhydrous base forms a resin. Two atoms of bromine may be added; the dibromide thus obtained is converted by alcoholic potash into *tetradehydrocinchene:*

$$\underset{\text{Dehydrocinchene dibromide}}{C_{19}H_{18}N_2Br_2} \longrightarrow \underset{\text{Tetradehydrocinchene}}{C_{19}H_{16}N_2} + 2HBr.$$

When cinchene is heated for several hours with 8–9 parts of concentrated sulphuric acid, there is formed in addition to cinchene sulphonic acids a *sulphocinchene,* $C_{19}H_{20}N_2SO_3$. If this derivative is oxidized with chromic acid, it is converted into cinchoninic acid and a sulphonic acid; on being heated to 170–180° with 25% phosphoric acid, it yields lepidine and a sulphonic acid. From these reactions it follows that the sulpho-group is not in the quinoline nucleus, but is attached to a carbon atom in the second half of the cinchene molecule.

When cinchene itself is heated with phosphoric acid it suffers hydrolytic dissociation into *lepidine* and *meroquinene:*



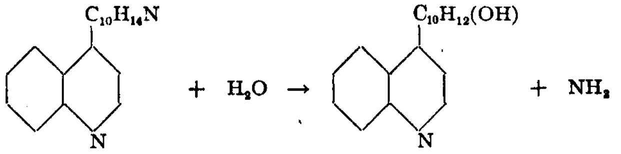
Cinchene   Lepidine

This decomposition is quite analogous to that which cinchonine experiences under the action of oxidizing agents.

Apocinchene.—While this last reaction appears fully to confirm the observations already presented regarding the constitution of cinchonine and the mode in which its two parts are united, a study of the action of the halogen acids on cinchene led

Königs to results which are not less interesting, but which it is difficult to coördinate satisfactorily with the preceding.

If cinchene is heated with hydrochloric or hydrobromic acid to 180–190°, it loses one of its nitrogen atoms as ammonia and yields an oxygenated body, *apocinchene*, of the formula $C_{19}H_{19}NO$. This substance crystallizes from alcohol in needles melting at 209°; it contains a hydroxyl group, since it yields with acetic anhydride an acetyl derivative. If apocinchene is treated with sodium nitrite and acetic acid, there is formed a *nitroapocinchene*, $C_{19}H_{18}(NO_2)ON$, which may be reduced to an *amidoapocinchene*, $C_{19}H_{18}(NH_2)ON$. Chromic acid converts both apocinchene and amidoapocinchene into cinchoninic acid. The reaction, accordingly, which leads to the formation of apocinchene does not affect the quinoline nucleus, but eliminates the nitrogen of the second half of the molecule and replaces it by a hydroxyl group:



Cinchene Apocinchene

Apocinchene possesses the properties of a phenol. It dissolves in caustic alkalies and is precipitated from the solution by carbonic acid; heated with alkyl halides and caustic potash, it yields esters. These phenol-like properties indicate that the hydroxyl of apocinchene is in an aromatic ring, and since we have proved that it is not contained in the benzol ring of the quinoline nucleus, it is necessary to assume the presence of a second ring of this character in the group $C_{10}H_{12}OH$.

Now the investigations of Königs [51] on the derivatives of apocinchene have shown that this second benzol ring is attached to the γ-carbon atom of the quinoline nucleus; they have, furthermore, made it appear highly probable that apocinchene contains

[51] Königs, J. pr. [2] 61, 1.

two side-chains which are ethyl groups. Apocinchene would then be a quinolyl-diethylphenol:

$$\begin{array}{l} C_6H_2\left\langle\begin{array}{l} C_2H_5 \\ C_2H_5 \\ OH \end{array}\right. \\ | \\ C_9H_6N \end{array}$$

Apocinchene

As a starting-point in these investigations Königs employed not apocinchene itself, but its ethyl ester, which, as has already been indicated, is readily obtained by treating apocinchene with ethyl iodide and caustic potash.

Ethylapocinchene, $C_{21}H_{23}NO$, crystallizes from alcohol in prisms which melt at 70–71°. It is a weak base. On oxidation with nitric acid or potassium permanganate it yields a monobasic acid, *ethylapocinchenic acid*, $C_{20}H_{19}NO_3$ (needles, melting-point 163–164°). The formation of this acid has accordingly been effected by the conversion of an ethyl group into a carboxyl:

$$(C_9H_6N)—C_6H_2\left\langle\begin{array}{l} C_2H_5 \\ C_2H_5 \\ OC_2H_5 \end{array}\right. \qquad (C_9H_6N)—C_6H_2\left\langle\begin{array}{l} COOH \\ C_2H_5 \\ OC_2H_5 \end{array}\right.$$

Ethylapocinchene Ethylapocinchenic acid

By heating ethylapocinchenic acid with hydrobromic acid to 130° we can eliminate the carboxyl group; the ethoxyl group is at the same time saponified and we obtain a lower homologue of apocinchene, ***homoapocinchene*** (Königs):

$$(C_9H_6N)—C_6H_2\left\langle\begin{array}{l} COOH \\ C_2H_5 \\ OC_2H_5 \end{array}\right. + HBr \rightarrow$$

Ethylapocinchenic acid

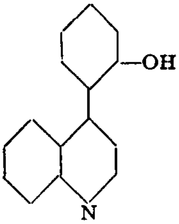
$$(C_9H_6N)—C_6H_3\left\langle\begin{array}{l} C_2H_5 \\ OH \end{array}\right. + C_2H_5Cl + CO_2.$$

Homoapocinchene

In its properties homoapocinchene resembles apocinchene; it is deposited from its alcoholic solution in crystals melting at 184–185°.

To eliminate from homoapocinchene the remaining ethyl group, Königs converted the base into its ester and then treated the latter with an oxidizing agent (lead or manganese dioxide and sulphuric acid). He thus obtained *ethylhomoapocinchenic acid*, $(C_9H_6N)—C_6H_3\left\langle\begin{array}{l}COOH\\OC_2H_5\end{array}\right.$ (melting-point 253–254°). When the silver salt of this acid is heated to 290°, there results *quinolylphenetol*, $(C_9H_6N)—C_6H_4OC_2H_5$. Finally on saponification with hydrobromic acid, the phenetol yields *γ-phenol quinoline*, $(C_9H_6N)—C_6H_4—OH$ (melting-point 208°).

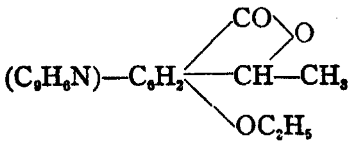
Now a derivative of this character can occur in three isomeric forms according to the position which the hydroxyl takes with respect to the quinoline nucleus. We have already seen (page 100) that these three isomers have been synthesized and that the ortho-derivative



is identical with the decomposition-product obtained from apocinchene.

The position of the hydroxyl being thus established, it remains to determine that of the two side-chains in apocinchene. The following observation offers the first suggestion of a solution of this.

When ethylapocinchenic acid is oxidized with lead peroxide and sulphuric acid, it yields a lactone:

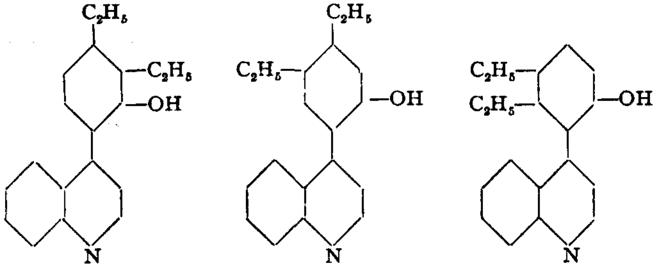


The action of bromine in alkaline solution decomposes this lactone into carbon tetrabromide and a dibasic acid, which melts at 230–240° and which is none other than a *quinolylphenetol dicarboxylic acid:*

$$(C_9H_6N)-C_6H_2\begin{cases}COOH\\COOH\\OC_2H_5\end{cases}$$

Now acetyl chloride converts this acid into an anhydride, which on being heated with resorcin forms a fluoresceïn; consequently the two carboxyls must stand in an ortho-position and so also the ethyl groups in apocinchene.

There is possible then for apocinchene only one of the following three formulæ:



Apocinchene

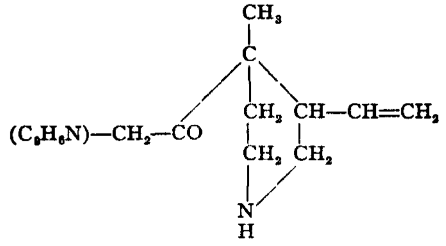
The question now arises as to whether the grouping of atoms found in apocinchene exists in the molecule of cinchonine—whether, in other words, the alkaloid itself is a derivative of γ-phenylquinoline. If such be the case, we must assume that the piperidine ring in the "second half" of cinchonine is associated with the benzol ring to form some such a complex as the quinoline or isoquinoline. But it is difficult to reconcile this with the results of the investigations of von Miller and Rohde.

It seems simpler to consider that the benzol nucleus of apocinchene exists neither in cinchonine nor in cinchene, but that

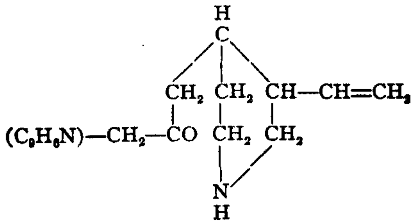
it is formed in the action of the halogen acids on the latter compound. It would then result from a sort of intramolecular condensation of that part of the piperidine nucleus which remained after the elimination of the nitrogen.

Such a reaction can scarcely be explained, however, if we adopt for cinchonine the formula of von Miller (page 354); but it becomes readily intelligible, we believe, on the basis of the formula which we have already suggested (page 355). This view is also supported by Königs.[52]

Such a formula for cinchonine is, moreover, in perfect accord with the probable constitution of cincholpoionic acid (formula I, page 348). On the other hand we must not fail to note that cinchotoxine with amyl nitrite yields not a *di-* but only a ***mono-***isonitroso-derivative—a reaction which finds most ready solution apparently in the formula of von Miller.[53]



Cinchotoxine (von Miller)



Cinchotoxine (Königs)

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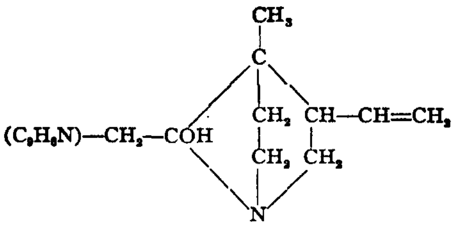
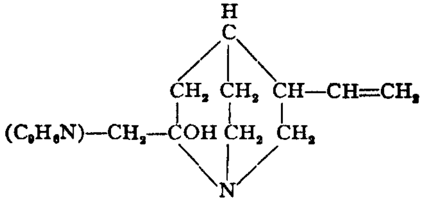
[52] Königs, J. pr. [2] 61, 1.
[53] von Miller and Rohde, B. 33, 3214.

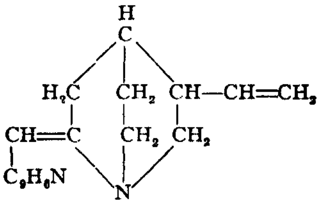


Cinchonine (von Miller)



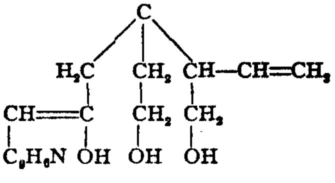
Cinchonine (Königs)

Taking, however, the constitution of Königs as the more probable, we derive the following for cinchene:

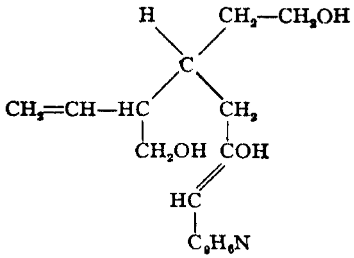


Cinchene

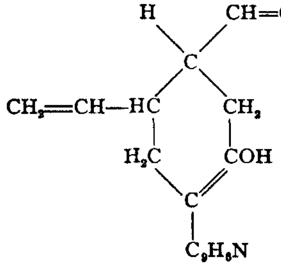
We may now assume that in the conversion of cinchene into apocinchene three molecules of water take part in the reaction; three atoms of hydrogen are eliminated with the nitrogen as ammonia and the three hydroxyls saturate the three carbon valences which were before attached to the nitrogen. In the first stage of the reaction there would then be formed the derivative



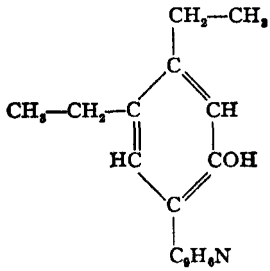
which may also be written in the following way:



This body is unstable and by loss of two molecules of water yields



Now it is not unreasonable to suppose that this cyclohexene derivative, with its two unsaturated side-chains, would exhibit a tendency, through a migration of four hydrogen atoms, to pass spontaneously into a true benzol derivative with saturated side-chains. We thus obtain the following formula for apocinchene:



Apocinchene

This is also one of the formulæ which Königs proposed for apocinchene.

2. CINCHONIDINE.

Cinchonidine, $C_{19}H_{22}N_2O$, was discovered by Winckler[54] in 1848; it was at first confused with quinidine. Pasteur[55] then called attention to the difference between the two alkaloids, gave cinchonidine its name, and showed its isomerism with cinchonine.

Cinchonidine accompanies quinine in all the cinchona-barks; in the extraction of the alkaloids it separates chiefly with quinidine.

It crystallizes from alcohol in prisms which melt at 207° and which are very little soluble in water. Its solutions are lævorotatory. As a febrifuge it is almost as active as quinine and is less poisonous. It gives no coloration with chlorine water and ammonia; its salt solutions are not fluorescent. The base is diacid and bitertiary and contains a hydroxyl group (monacetyl derivative).[56]

Cinchonidine is a stereoisomer of cinchonine. By prolonged boiling of cinchonine with a solution of caustic potash in amyl alcohol, Königs and Husmann[57] succeeded in converting a part of the alkaloid into cinchonidine. The simple relation subsisting between the two bases is shown, moreover, in the similarity of their reactions and in the identity of the most of their transformation- and decomposition-products.

When cinchonidine is heated with glycerine to 200°, or with dilute sulphuric acid to 130°, it is converted into the same *cinchonicine* (cinchotoxine) into which cinchonine is transformed under like conditions (Pasteur). Other isomers (*β-cinchonidine, γ-cinchonidine, homocinchonidine, apocinchonidine, isocinchonidine*, etc.) are formed by the action of mineral acids or of alkalies.[58]

[54] Winckler, *Repertorium der Pharmacie*, **85**, 392; **98**, 384; **99**, 1.

[55] Pasteur, *Journal de pharmacie*, [3] **23**, 123.

[56] Hesse, A. **205**, 196.

[57] Königs and Husmann, B. **29**, 2185.

[58] Hesse, A. **205**, 196; **243**, 131; **258**, 133; **276**, 125. Skraup, B. **25**, 2909. Neumann, M. **13**, 651.

Cinchonidine contains an ethylene bond; it adds a molecule of hydrogen chloride, bromide, or iodide. Two isomeric dibromcinchonidines have been prepared.[59] Reduction with sodium and alcohol converts the alkaloid into a tetrahydro-derivative, a secondary base.[60]

Fusion with caustic potash gives rise to quinoline.[61] On oridation with potassium permanganate in acid solution there are formed formic acid and a base, isomeric with cinchotenine, *cinchotenidine*, $C_{18}H_{20}N_2O_3$ (prisms, containing three molecules of water and soluble in alkalies and acids, lævorotatory; melting-point 256°).[62]

With stronger oxidizing agents (nitric or chromic acid) cinchonidine yields the same products as cinchonine, viz., cinchoninic and cincholoiponic acids.[63] On treating cinchonidine with phosphorus pentachloride Königs and Comstock [64] obtained a cinchonidine chloride, $C_{19}H_{21}N_2Cl$ (melting-point 108–109°), an isomer of cinchonine chloride; alcoholic potash converts both chlorides into cinchene.

On reduction with iron and dilute sulphuric acid cinchonidine chloride yields *desoxycinchonidine*, $C_{19}H_{22}N_2$ (melting-point 61°, lævorotatory), an isomer of *desoxycinchonine*.[65] *Methyldesoxycinchonine* and *methyldesoxycinchonidine* are however identical.[66]

These observations indicate that the difference between cinchonine and cinchonidine is occasioned solely by the asymmetry of that carbon atom to which the hydroxyl group is attached. Furthermore, it follows that both alkaloids are tertiary alcohols with the grouping ≡C—OH (and not=CHOH), since their isomerism persists after replacing the hydroxyl with hydrogen

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[59] Galimard, Bl. [3] 25, 84.
[60] Konek von Norwall, B. 29, 801.
[61] Leers, A. 82, 147.
[62] Skraup and Vortmann, A. 197, 226. Schniderschitsch, M. 10, 51.
[63] Skraup, A. 201, 300. Skraup and Würstl, M. 10, 220.
[64] Königs and Comstock, B. 17, 1984.
[65] Königs, B. 29, 372.
[66] Königs, B. 31, 2355.

—a condition which could not obtain if this asymmetric carbon atom were already attached to a hydrogen atom.

3. CINCHOTINE.

Cinchotine or *hydrocinchonine*, $C_{19}H_{24}N_2O$, was isolated by Caventou and Willm[67] in 1869. It is found in crude cinchonine, but only in small quantity; the best yield is obtained from the cinchonine which is derived from the bark of *Remijia purdieana.*[68] Cinchotine is isolated by treating crude cinchonine in the cold with potassium permanganate, which destroys the latter alkaloid, but only slightly attacks the former.

Von Arlt[69] has shown that the *pseudocinchonine* of Hesse[70] is identical with cinchotine.

As indicated by Jungfleisch[71] and Léger, *cinchonifine* (page 344) is also probably identical with cinchotine.

Cinchotine crystallizes in prisms which melt at 286°; it is dextrorotatory and bitertiary. Unlike cinchonine it is a saturated derivative; its salts form no addition-products with hydrogen chloride or iodide.[72]

By the action of concentrated sulphuric acid, the alkaloid is converted into a *cinchotine sulphonic acid*, $C_{19}H_{23}N_2O \cdot SO_3H$.[68,73] In this acid the SO_3H group is probably attached to the "second half" of the molecule.[74] With acetic anhydride an acetyl derivative is formed.[68] Oxidation with chromic acid gives rise to *cinchoninic acid* and *cincholoipone*, $C_9H_{17}NO_2$.[75]

Phosphorus pentachloride acts upon cinchotine, producing the chloride $C_{19}H_{23}ClN_2$ (melting-point 85–87°), which with

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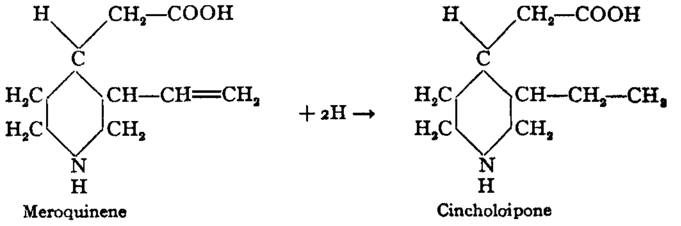
[67] Caventou and Willm, A. Suppl. 7, 247.
[68] Hesse, A. 300, 42.
[69] von Arlt, M. 20, 425.
[70] Hesse, A. 276, 106.
[71] Jungfleisch and Léger, C. r. 132, 410.
[72] Skraup, B. 28, 12. Hesse, B. 28, 1298.
[73] Skraup, A. 300, 357; M. 18, 414.
[74] Schmid, M. 22, 803.
[75] Skraup, M. 9, 783; 10, 39, 220.

alcoholic potash yields *dihydrocinchene*, $C_{19}H_{22}N_2$ (crystals, melting-point 145°). The latter derivative differs from desoxycinchonine (page 357); it is decomposed by phosphoric acid into lepidine and cincholoipone.[76]

Cincholoipone is deposited from its solution in methyl alcohol in crystals which melt at 236°; it is lævorotatory and possesses the character of a secondary base (nitrosamine, acetyl derivative), and also that of a monobasic acid; with alcohol and hydrochloric acid it yields an ester.[77]

Cincholoipone, like cinchotine, is a saturated derivative; it is neither reduced by sodium amalgam nor hydriodic acid at 180°; chromic acid oxidizes it to cincholoiponic acid. Distillation of its hydrochloride with zinc-dust gives rise to β-lutidine.

Cincholoipone is closely related to meroquinene. This is shown by its formation, when the latter is reduced in the cold with zinc-dust and concentrated hydriodic acid:[78]

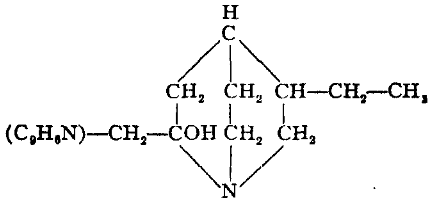


From all these reactions it is apparent that cinchotine and cinchonine exhibit an extended parallelism. With the various decomposition-products of cinchonine corresponds a series of analogous derivatives of cinchotine which differ from the former, member for member, only in containing two more atoms of hydrogen:

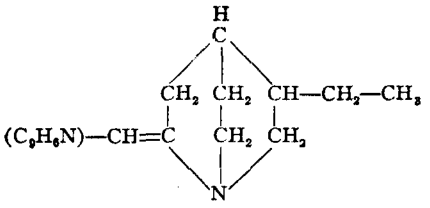
Cinchonine	$C_{19}H_{22}N_2O$.	Cinchotine	$C_{19}H_{24}N_2O$.
Cinchene	$C_{19}H_{20}N_2$.	Dihydrocinchene	$C_{19}H_{22}N_2$.
Meroquinene	$C_9H_{15}NO_2$.	Cincholoipone	$C_9H_{17}NO_2$.

76 Königs, B. 27, 1501, 2290.
77 Skraup, M. 16, 159.
78 Königs, B. 35, 1349.

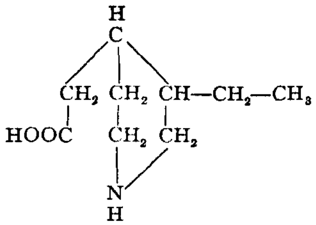
From the relation of cincholoipone to meroquinene it naturally follows that the vinyl group $—CH=CH_2$ of cinchonine is in cinchotine replaced by the ethyl group $—CH_2—CH_3$. We thus derive the following formulæ:



Cinchotine



Dihydrocinchene



Cincholoipone

4. Cinchamidine.

Cinchamidine or hydrocinchonidine, $C_{19}H_{24}N_2O$, was isolated by Hesse [79] in 1881. It occurs in the form of leaflets and melts at 230°; it is lævorotatory and contains a hydroxyl group (acetyl derivative); it gives no addition-product with hydrogen chloride. Chromic acid oxidizes it to cinchoninic acid.

5. Cinchonamine.

This base, $C_{19}H_{24}N_2O$, is found in largest quantities in the *Remijia*-barks and particularly in that of *Remijia purdieana* Wedd. Cinchonamine was isolated by Arnaud [80] in 1881. It

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[79] Hesse, A. **214**, 1.

[80] Arnaud, C. r. **93**, 593; **97**, 174; **98**, 1488; **99**, 190; A. ch. [6] **19**, 93.

is a dextrorotatory body which crystallizes in needles (melting-point 184–185°); it contains a hydroxyl group (acetyl derivative). It is attacked in the cold by a solution of potassium permanganate and therein differs characteristically from the two alkaloids mentioned above, with which it corresponds in composition. The double salts of cinchonamine have been carefully studied.[81] The alkaloid acts as a strong febrifuge, but it is also very poisonous.

6. CUPREÏNE.

Cupreïne was discovered by Paul and Cowley[82] in 1884 in the bark of *Remijia pedunculata;* it is there found in small quantity in molecular combination with quinine (page 373). It crystallizes from ether in prisms containing two molecules of water of crystallization; the anhydrous alkaloid melts at 198°; it is little soluble in ether and chloroform; more readily soluble in alcohol. It is a diacid and bitertiary base, lævorotatory and little poisonous; with chlorine and ammonia it gives the reaction of quinine, but its solution in sulphuric acid does not fluoresce.

The formation of a *diacetylcupreïne* shows that the two oxygen atoms of cupreïne are contained in the base as hydroxyls.[83] One of these hydroxyl groups has a phenol character, for of all the cinchona alkaloids cupreïne alone dissolves in alkalies to form salts. These contain one atom of metal and are decomposed by carbonic acid.

When cupreïne is heated with hydrochloric acid to 140° it is converted into an isomer, *apoquinine* (Hesse). Apoquinine is also obtained together with methyl chloride when quinine is subjected to the same treatment. This reaction leads one to believe that the relation between cupreïne and quinine is that of a phenol to its ester:

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[81] Bontroux and Genoresse, C. r. 125, 467.
[82] Paul and Cownley, *Pharmaceutical Journal,* [3] 15, 221, 401.
[83] Hesse, A. 230, 57.

Cupreïne................ $C_{19}H_{20}N_2(OH)_2$
Quinine................ $C_{19}H_{20}N_2(OH)(OCH_3)$

This simlpe relation between the two alkaloids was established in 1891 by Grimaux and Arnaud;[84] by heating a methyl alcohol solution of cupreïne with sodium methylate and methyl iodide they effected the synthesis of quinine:

$$\underset{\text{Sodium salt of cupreïne}}{C_{19}H_{20}N_2(OH)(ONa)} + CH_3I \rightarrow \underset{\text{Quinine}}{C_{19}H_{20}N_2(OH)(OCH_3)} + NaI.$$

What we shall say later on regarding the constitution of quinine will accordingly apply to that of cupreïne.

Cupreïne probably differs from cinchonine only in having an additional hydroxyl group in the para-position of the quinoline ring.

7. Quinamine.

Quinamine, $C_{19}H_{24}N_2O_2$, was found by Hesse[85] in 1872 in different cinchona-barks; it crystallizes from alcohol in long prisms, which melt at 172°; it is dextrorotatory and readily oxidizable.

Hydrochloric and sulphuric acids remove from it a molecule of water and convert it into *apoquinamine*, $C_{19}H_{22}N_2O$, a weak base, which crystallizes in leaflets or in prisms and melts at 114°. In neutral solution it is optically inactive, in acid lævorotatory. Acetic anhydride also dehydrates quinamine; there results the monacetyl derivative of apoquinamine, *acetapoquinamine*, $C_{21}H_{24}N_2O_2$, an amorphous substance. From this it follows that quinamine contains two hydroxyl groups.

8. Conquinamine.

This base, $C_{19}H_{24}N_2O_2$, accompanies the isomeric quinamine in the bark of *Remijia pedunculata*, from which Hesse[86] obtained

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[84] Grimaux and Arnaud, C. r. **112**, 766, 1364; **114**, 548, 672.
[85] Hesse, A. **166**, 266; **207**, 288.
[86] Hesse, A. **209**, 62.

it in 1877. It is a crystalline derivative, dextrorotatory, easily oxidizable, and melting at 123°.[87]

9. Quinine.

Quinine, by virtue of its remarkable febrifugal, antiseptic, and tonic properties is by far the most important of the cinchona alkaloids.

It was isolated by Pelletier and Caventou [88] in 1820 at the same time as cinchonine. Its composition, established by Strecker [89] in 1854, corresponds with the formula $C_{20}H_{24}N_2O_2$.

In 1891 Grimaux and Arnaud,[90] as we have already shown (page 372), effected a partial synthesis of quinine from cupreïne by introducing in this alkaloid a methyl group in place of the hydrogen of the phenol group. This synthesis of theoretical interest is of little practical importance, since cupreïne is only found in small quantities in certain cinchona-barks.

Quinine is precipitated from its salt solutions by alkalies in an amorphous and anhydrous condition, but it soon assumes a crystalline form and yields a hydrate with three molecules of water. Under certain conditions it can also form hydrates with one or two and even with eight or nine molecules of water.[91] Quinine may also be obtained in anhydrous crystals (small needles) by treating a warm solution of one of its salts with sodium carbonate;[92] anhydrous quinine melts at 173°, the trihydrate at 57°.

The base is little soluble in water and ligroin; it dissolves readily in alcohol and ether, less readily in chloroform, and with difficulty in benzol. Solutions of quinine possess a bitter taste, an alkaline reaction, and are lævorotatory.

Some of its salts, particularly the sulphate, give a blue fluo-

[87] Oudemans, A. **209**, 38.
[88] Pelletier and Caventou, A. ch. [2] **15**, 291, 337.
[89] Strecker, C. r. **39**, 58.
[90] Grimaux and Arnaud, C. r. **112**, 774; **114**, 672.
[91] Hesse, A. **135**, 325.
[92] Hesse, B. **10**, 2153.

rescence in aqueous solution. The free base yields with ammonia and chlorine water a characteristic green color.

Quinine is a diacid and bitertiary base; it forms a diethiodide [93] and two isomeric monomethiodides.[94]

It possesses a hydroxyl and a methoxyl group. The presence of a hydroxyl is shown by the formation of a *monobenzoylquinine* [95] and a *monacetylquinine;* [96] the methoxyl is indicated by the evolution of methyl chloride or iodide, when quinine is heated with concentrated hydrochloric or hydriodic acid to 140–150° [96] [97]; there is obtained in this reaction at the same time *apoquinine*, $C_{19}H_{22}N_2O_2 + 2H_2O$, a crystalline body, lævorotatory and melting at 210°. Apoquinine still gives with chlorine and ammonia the reaction for quinine, but its salt solutions do not fluoresce.

Apoquinine is soluble in alkalies and yields a diacetyl derivative; this indicates that it contains two hydroxyls, of which one possesses the nature of a phenol. The decomposition of quinine by hydrochloric acid may accordingly be expressed by the following equation:

$$\underset{\text{Quinine}}{C_{19}H_{20}N_2(OH)(OCH_3)} + HCl \rightarrow \underset{\text{Apoquinine}}{C_{19}H_{20}N_2(OH)_2} + CH_3Cl.$$

Apoquinine is an isomer of cupreïne (page 371); it is also formed, when cupreïne is heated with hydrochloric acid to 140°.[98] Very probably the first product of the action of hydrochloric acid on quinine is cupreïne, which is then converted into its isomer.

Quinine is an unsaturated body. Zinc and sulphuric acid reduce it to *dihydroquinine*, $C_{20}H_{26}N_2O_2$.[99] Sodium and alcohol give rise to *tetrahydroquinine*, $C_{20}H_{28}N_2O_2$.[100] It adds two atoms

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[93] Strecker, C. r. 39, 58. Claus and Mallmann, B. 14, 76.
[94] Skraup and Konek von Norwall, B. 26, 1968; M. 15, 37.
[95] Schützenberger, C. r. 47, 81, 233.
[96] Hesse, A. 205, 314.
[97] Lippmann and Fleissner, M. 16, 34.
[98] Hesse, A. 230, 55.
[99] Schützenberger, A. 108, 347.
[100] Lippmann and Fleissner, M. 16, 630. Konek von Norwall, B. 29, 801.

of bromine or a molecule of hydrogen halide.[101] The derivatives with the halogen acids are decomposed by alkalies, but quinine is only in part reformed; the greater portion is converted into isomeric derivatives (isoquinine, pseudoquinine, niquine, etc).[102]

Other isomers are formed from quinine by the action of sulphuric acid or simply by the action of heat on the alkaloid. The best known of these is *quinicine*, which Pasteur [103] obtained in 1853 by heating quinine with very dilute sulphuric acid to 120–130°. It forms a resinous mass melting at about 60°, is bitter in taste, and possesses febrifugal properties; with chlorine and ammonia it gives a somewhat lighter green coloration than does quinine; unlike the latter alkaloid, however, its salt solutions do not fluoresce and they turn the plane of polarized light to the right. Howard [104] claims that he has detected quinicine in some cinchona-barks. According to Fussenegger [105] quinicine is identical with *quinotoxine*.

Fusion with caustic potash decomposes quinine into products similar to those derived from cinchonine; there are formed *β*-lutidine and lower fatty acids, but in place of quinoline and lepidine there result *quinolidine* [106] (*p*-methoxyquinoline, page 87) and *p-methoxylepidine* (page 95).[107]

By the moderate oxidation of quinine with potassium permanganate at a low temperature an atom of carbon is split off as formic acid and we obtain *quitenine*, $C_{19}H_{22}N_2O_4+4H_2O$.[108] This crystallizes in prisms which lose their water of crystallization at 110° and on being rapidly heated melt at 286°. It is a weak base, lævorotatory, soluble in alkalies; it is converted into an

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[101] Comstock and Königs, B. **20**, 2510; **25**, 1539.

[102] Hesse, A. **276**, 125. Skraup, M. **12**, 667; **14**, 428; B. **25**, 2909. Lippmann and Fleissner, B. **24**, 2827; M. **12**, 327; **13**, 429; **14**, 553.

[103] Pasteur, C. r. **37**, 110, 166.

[104] Howard, Soc. **24**, 61; **25**, 101.

[105] Fussenegger, B. **33**, 3214.

[106] Butlerow and Wischnegradsky, B. **11**, 1254; **12**, 2094.

[107] Königs, B. **23**, 2669.

[108] Kerner, *Zeitschrift für Chemie*, **5**, 593. Skraup, B. **12**, 1104; A. **199**, 348; M. **10**, 39.

ester by alcohol and hydrochloric acid; it forms no addition-product with hydrogen iodide. We must, accordingly, assign to it a constitution similar to that of cinchotenine and assume that it is formed by the conversion of a $—CH{=}CH_2$ group into a carboxyl group.[109] When quitenine is heated with hydriodic acid, it is decomposed into methyl iodide and *quitenol*, $C_{18}H_{20}N_2O_4$; this bears the same relation to quitenine as apoquinine to quinine.

A stronger oxidizing agent (nitric acid, or potassium permanganate at a higher temperature) converts quinine as it does cinchonine (page 345) into cinchomeronic and α-carbocinchomeronic acids.[110]

On oxidizing quinine with chromic acid, Skraup[111] obtained *cincholoiponic acid* and an acid of the formula $C_{11}H_9NO_3$, which he named *quininic acid.* As we have seen (page 105), the latter acid is the *p*-methoxy-derivative of cinchoninic acid.

The action of phosphorus pentachloride on quinine leads to the formation of derivatives analogous to those which are obtained from cinchonine.[112] There results a *quinine chloride*, $C_{20}H_{23}ClN_2O$ (crystals, melting at 151°), which alcoholic potash converts into *quinene*, $C_{20}H_{22}N_2O$ (melting-point 81–82°). The latter is the *p*-methoxy-derivative of cinchene; by the action of phosphoric acid it is decomposed into meroquinene and *p*-methoxy-lepidine; on treatment with hydrobromic acid at 180°, it yields *apoquinene* (*p*-oxyapocinchene), $C_{19}H_{19}NO_2$.

From all these reactions it is evident that quinine and cinchonine are identical in the "second half" of the molecule. The difference lies only in the first half, which is a quinolyl radical in the case of cinchonine, while in the case of quinine it is the same radical with a methoxyl group in the para position.

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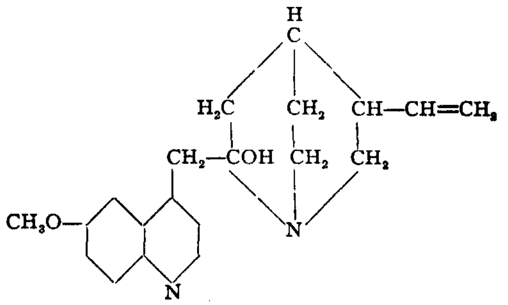
[109] Skraup, B. **28**, 12.

[110] Ramsay and Dobbie, Soc. **35**, 189. Weidel and Schmidt, B. **12**, 232, 1104, 1146.

[111] Skraup, M. **2**, 591; **4**, 695; **10**, 39, 220.

[112] Comstock and Königs, B. **17**, 1984; **18**, 1219; **20**, 2510, 2674. Königs, B. **23**, 2669; **27**, 900; **29**, 372.

Quinine is consequently *p-methoycinchonine* and we may assign to it the following constitutional formula:



Quinine

Analogous to the artificial preparation of quinine by forming the methyl ester of cupreïne, we may introduce other alkyl radicals and in this way secure the higher homologues of quinine. Thus Grimaux and Arnaud [113] obtained the following series:

Quinethyline........	$C_{19}H_{20}N_2(OH)OC_2H_5$,	melting-point	160°.
Quinpropyline.......	$C_{19}H_{20}N_2(OH)OC_3H_7$,	"	164°.
Quinisopropyline.....	$C_{19}H_{20}N_2(OH)OC_3H_7$,	"	154°.
Quinisoamyline......	$C_{19}H_{20}N_2(OH)OC_5H_{11}$,	"	167°.

These bodies are mostly amorphous, are strongly febrifugal, but are also more poisonous than quinine.

10. QUINIDINE.

Quinidine, $C_{20}H_{24}N_2O_2$, was discovered in 1833 by Henry and Delondre.[114] It was studied somewhat by Pasteur [115] and later more fully by Hesse,[116] who named it *conquinine*.

[113] Grimaux and Arnaud, C. r. **112**, 766, 1364; **114**, 548, 672; **118**, 1803.
[114] Henry and Delondre, *Journal de pharmacie*, [2] **19**, 623; **20**, 157.
[115] Pasteur, C. r. **32**, 110; **36**, 26; **37**, 110.
[116] Hesse, A. **146**, 357; **166**, 232; **205**, 318; **243**, 131.

This stereoisomer of quinine crystallizes from water, alcohol, or ether in combination with one molecule of the solvent; from benzol it separates in anhydrous needles which melt at 171.5°.

Quinidine is dextrorotatory and acts as a febrifuge; it is readily soluble in ether and alcohol, difficultly so in chloroform and very little in water. It gives the same color reactions as quinine.

The base contains an ethylene bond (addition-products with hydrogen chloride and iodide), a hydroxyl (monacetyl derivative) and a methoxyl group; concentrated hydrochloric acid at 140–150° decomposes it into methyl chloride and *apoquinidine*, $C_{19}H_{22}N_2O + 2H_2O$, an amorphous body, which is dextrorotatory and which contains two hydroxyl groups (diacetyl derivative).

Dilute sulphuric acid or glycerine at 180° converts quinidine into quinicine (Pasteur); phosphorus pentachloride and alcoholic potash into quinine;[117] chromic acid into quininic and cincholoiponic acids.[118]

All these derivatives are identical with those which quinine itself yields.

11. Hydroquinine.

Hydroquinine, $C_{20}H_{26}N_2O_2$, is found associated with quinine in the extraction of the latter alkaloid. It is separated from this alkaloid by treatment with potassium permanganate, which destroys the quinine, but does not affect the hydroquinine.

Hydroquinine was isolated by Hesse[119] in 1882. It crystallizes with two molecules of water and melts in the anhydrous condition at 172°; it is lævorotatory and contains a hydroxyl and a methoxyl group; with acetic anhydride it yields a monacetyl derivative; heated with hydrochloric acid to 150°, it is decomposed into methyl chloride and *hydrocupreïne*, $C_{19}H_{22}N_2(OH)_2$, a base which melts at 168–170° and is soluble in alkalies.

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[117] Comstock and Königs, B. **18**, 1219.

[118] Skraup, M. **2**, 587; **10**, 65, 220.

[119] Hesse, A. **241**, 255; B. **15**, 856; **28**, 1298.

12. Hydroquinidine.

This alkaloid, $C_{20}H_{26}N_2O_2$, is found in commercial quinidine and can be obtained from this by treatment with permanganate. It was isolated in 1881 by Forst and Böhringer.[120] It crystallizes in plates or in prismatic needles with two and one-half molecules of water; its melting-point is 166–167°; it is dextrorotatory. Hydrochloric acid acts upon the base at 150°, splitting off methyl chloride; oxidation with chromic acid converts it into quininic acid.

13. Chairamine,

$C_{22}H_{26}N_2O_4+H_2O$. Needles or prisms which in the hydrous condition melt at 140°, in the anhydrous at 233°. Dextrorotatory.

14. Chairamidine,

$C_{22}H_{26}N_2O_4+H_2O$. Amorphous, dextrorotatory; melting-point of the anhydrous alkaloid 126–128°.

15. Conchairamine,

$C_{22}H_{26}N_2O_4+H_2O$. A very weak base, dextrorotatory, melting in the anhydrous condition at 120°.

16. Conchairamidine,

$C_{22}H_{26}N_2O_4+H_2O$. Needles which melt in the anhydrous condition at 114–115°. Lævorotatory.

These last four alkaloids were isolated by Hesse [121] in 1884 from the bark of *Remijia purdieana*.

17. Aricine.

Aricine, $C_{23}H_{26}N_2O_4$, was discovered by Pelletier and Corriol [122] in Cusco-bark (*Cinchona pubescens* Wedd.) and its formula was

[120] Forst and Böhringer, B. 14, 1955; 15, 519, 1656.

[121] Hesse, A. 225, 211.

[122] Pelletier and Corriol, *Journal de pharmacie*, 15, 575; A. ch. [2] 51, 585.

determined by Gerhardt. It crystallizes from alcohol in prisms which melt at 188°. It is lævorotatory in neutral solution, inactive in hydrochloric acid.[123]

18. CUSCONINE.

This alkaloid, $C_{23}H_{26}N_2O_4 + 2H_2O$, is found in Cusco-bark [124] in connection with aricine.[123] It crystallizes in prisms melting at 110° and is lævorotatory.

19. CONCUSCONINE.

Concusconine, $C_{23}H_{20}N_2O_4 + H_2O$, occurs in the barks of *Remijia*.[125] It melts at 206–208° and is dextrorotatory.

20. HOMOQUININE.

Homoquinine was discovered by Paul and Cownley [126] in the bark of *Remijia pedunculata;* it was investigated by Hesse.[127] This investigator showed that homoquinine is an equimolecular combination of quinine and cupreïne, $C_{20}H_{24}N_2O_2 \cdot C_{19}H_{22}N_2O_2$. By the action of alkalies homoquinine is decomposed into a mixture of the two bases, while it may be synthesized from quinine and cupreïne, when an equimolecular mixture of these bases is treated with dilute sulphuric acid.

Homoquinine crystallizes from ether in leaflets which contain two molecules of water or in prisms which contain four. It is lævorotatory and melts in the anhydrous condition at 177°.

21. DIQUINIDINE, or DICONQUININE.

This base, $C_{40}H_{46}N_4O_3$, is found in all the cinchona species and forms the major part of *quinoidine*, the mass of amorphous cinchona alkaloids, which is obtained as a residue from the

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[123] Hesse, A. 181, 58; 185, 320.
[124] Leverköhn, *Repertorium der Pharmacie*, 33, 353.
[125] Hesse, B. 16, 58; A. 225, 211.
[126] Paul and Cownley, *Pharmaceutical Journal*, 1881, 599; 1884, 221, 279.
[127] Hesse, B. 15, 854; A. 225, 95; 226, 240; 230, 55.

crystallization of the sulphates. The base and its salts do not crystallize; they are dextrorotatory.[128]

Quinic Acid.

Of the many non-nitrogenous substances which are found in the cinchona-barks (page 338), quinic acid occurs in largest quantity (5–8%). It consequently seems not inadvisable briefly to consider this derivative.

Quinic acid was discovered in cinchona-barks by Hofmann[129] in 1790. Its formula as determined by Liebig[130] is $C_7H_{12}O_6$. It crystallizes in monoclinic prisms, is readily soluble in water, melts at 161.6°, and is lævorotatory.

It is a monobasic acid containing four alcoholic hydroxyls; by the action of acetyl chloride its esters are converted into tetra-acetyl derivatives.[131] The acid may consequently be formulated as follows:

$$C_6H_7(OH)_4COOH.$$

It is highly probable that quinic acid is a derivative of a hexahydro-benzol. All its decomposition-products are in fact aromatic derivatives. Dry distillation decomposes the acid into hydroquinone, phenol, benzol, benzoic acid, and salicylaldehyde.[132] Heating of its salts gives rise to quinone;[133] oxidation with manganese dioxide and sulphuric acid yields the same result. When quinic acid is boiled with hydrochloric acid, it forms hydroquinone and *p*-oxybenzoic acid.[134] Phosphorus pentachloride converts the acid into *m*-chlorbenzoyl chloride.[135]

According to all these reactions quinic acid appears to be best represented as a *hexahydro-tetraoxybenzoic acid.*

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[128] Hesse, B. 10, 2155; 16, 58.
[129] F. C. Hofmann, *Crell's Annalen*, 2, 314.
[130] Liebig, *Annalen der Physik und Chemie*, 21, 1; A. 6, 14.
[131] Fittig and Hillebrand, A. 193, 197. Erwig and Königs, B. 22, 1457.
[132] Wöhler, A. 45, 354; 51, 146.
[133] Woskresensky, A. 27, 257.
[134] Hesse, A. 200, 238.
[135] Graebe, A. 138, 197; 146, 66.

CHAPTER XXVIII.

THE STRYCHNOS ALKALOIDS.

THE plants of the genus Strychnos (family of the Loganiaceæ) yield *strychnine*, *brucine*, *strychnicine* (?), and several *curare* alkaloids.

The nux vomica, the seed of *Strychnos Nux-vomica* L., contains about 1.5% strychnine and about the same amount of brucine; the "false Angustura-bark" from the same tree shows nearly the same alkaloidal content, as do also the seeds of *Strychnos Ignatii* Berg., the so-called "St. Ignatius' beans." Both these alkaloids are found, furthermore, in the woody root of *Strychnos colubrina* L., and in that of *Strychnos Tieuté* Lesch.

Curare, the dark, resinous extract of several species of Strychnos, particularly of *Strychnos toxifera* Bent., and *Strychnos castelnaca* Wedd., contains a number of poisonous bases, *tubocurarine*, *curine*, *curarine*, *protocurine*, *protocuridine*, and *protocurarine*.

By many of the Indians of South America curare is used as an arrow-poison. It appears to be a virulent poison only when administered through the skin. It paralyzes the motor nerves and kills by suffocation.

1. STRYCHNINE.

Strychnine was discovered in "St. Ignatius' beans" by Pelletier and Caventou[1] in 1818. Its composition is represented by the formula $C_{21}H_{22}N_2O_2$. It crystallizes from alcohol in prisms which melt at 269°. It is almost insoluble in water and is difficultly soluble in the ordinary organic solvents. In its

[1] Pelletier and Caventou, A. ch. [2] 10, 142; 26, 44.

action on polarized light, it is lævorotatory. Its taste is very bitter and at the same time metallic; its physiological properties class it among the most powerful of all known poisons.

Strychnine shows an alkaline reaction; it is a tertiary, mon-acid base, and accordingly forms salts with only one molecule of acid, although it contains two nitrogen atoms in the molecule.[2]

The action of hydrochloric acid at 100° does not occasion the elimination of methyl chloride;[3] strychnine, consequently, contains no methoxyl group.

Sulphuric acid, nitric acid, and the halogens form substitution-products;[4] this leads one to suspect the presence of an aromatic ring in the molecule.

Oxidizing agents readily attack strychnine, but the various products obtained have as yet thrown but little light on the constitution of the alkaloid. Potassium ferricyanide gives rise to an oxystrychnine,[5] $C_{21}H_{22}N_2O_3$; potassium permanganate to strychnic * acid, $C_{11}H_{11}NO_3+H_2O$, an amorphous body possessing both acid and basic properties.[6] Chromic acid converts strychnine into an acid of the formula $C_{16}H_{18}N_2O_4+2H_2O$. This acid melts at 285° with the evolution of carbon dioxide,[7] and on distillation with zinc-dust yields (according to Loebisch and Schoop[8]) carbon dioxide, acetylene, and carbazol. The formation of carbazol also points to the presence of an aromatic ring in the molecule of strychnine.

Fusion with caustic potash converts strychnine into quinoline bases, butyric acid, and indol.[9] Distilled with lime the alkaloid yields ammonia, ethylamine, ethylene, β-picoline, β-lutidine,

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[2] Scholtz, B. **31**, 1700.

[3] Shenstone, Soc. **43**, 101; **47**, 139.

[4] Minunni and Ortoleva, G. **30**, I, 39.

[5] Beckurts, *Pharmaceutische Centralhalle*, 1881, 325.

[6] Hanriot, C. r. **96**, 1671.

[7] Hanssen, B. **17**, 2849; **18**, 777, 1917; **20**, 451.

[8] Loebisch and Schoop, M. **7**, 609.

[9] Goldschmidt, B. **15**, 1977. Loebisch and Schoop, M. **7**, 75.

* The name strychnic is here used instead of strychninic to avoid confusion with another derivative which bears the latter title.

skatol, and carbazol.[10] Distillation with zinc-dust gives rise to similar products: ammonia, ethylene, acetylene, lutidine, carbazol.[8, 11]

Strychnol (Strychninic Acid).—When strychnine is heated with alcoholic soda it adds a molecule of water and yields strychnol:[12]

$$\underset{\text{Strychnine}}{C_{21}H_{22}N_2O_2} + H_2O \rightarrow \underset{\text{Strychnol}}{C_{21}H_{24}N_2O_3}.$$

This derivative, which has been studied chiefly by Tafel, affords us the most reliable data yet obtained regarding the constitution of strychnine.

Strychnol crystallizes with four molecules of water in needles which melt at 215°. It dissolves in alkalies and is reprecipitated from its solutions by carbonic acid. It is not, however, a phenol, as it was formerly supposed to be, when it received the name of "strychnol," but is a true carboxylic acid. Tafel accordingly gives it the name *strychninic acid.*

Strychninic acid differs from strychnine in that it possesses a carboxyl and an imide group; it is consequently an imidocarboxylic acid. Tafel explains the conversion of strychnine into the acid by assuming that the former contains the group $<\!\begin{array}{l}CO\\ |\\ N\end{array}$, which by the absorption of water passes into the grouping $<\!\begin{array}{l}COOH\\ NH\end{array}$:

$$\underset{\text{Strychnine}}{N{\equiv}C_{20}H_{22}O\!<\!\begin{array}{l}CO\\ |\\ N\end{array}} + H_2O \rightarrow \underset{\text{Strychnol (strychninic acid)}}{N{\equiv}C_{20}H_{22}O\!<\!\begin{array}{l}COOH\\ NH\end{array}}$$

Strychnol is a secondary tertiary base; its imide nature is shown from the formation of a nitrosamine. Strychnol does not

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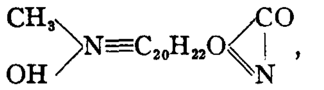
[10] Stöhr, B. 20, 810, 1108, 2727; J. pr. 42, 399. Loebisch and Malfatti, M. 9, 626.

[11] Scichilone and Magnanini, G. 12, 444.

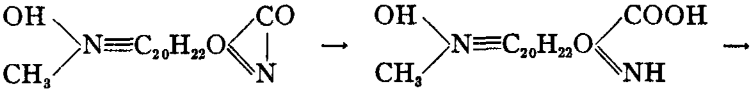
[12] Tafel, B. 23, 2731; A. 264, 33; 268, 229; 301, 285; 304, 49.

yield an ester in the presence of mineral acids, since the latter reconvert it into strychnine. The presence of the carboxyl group is, however, indicated by the conversion of the more stable *methylstrychnine methiodide*, $\genfrac{}{}{0pt}{}{CH_3}{I}\rangle N{\equiv}C_{20}H_{22}O\langle\genfrac{}{}{0pt}{}{COOH}{NCH_3}$, into its ester by treatment with methyl alcohol and hydrochloric acid.

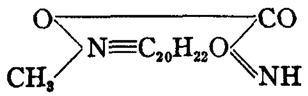
The relation of strychnine to strychnol is further revealed by the action of the alkyl halides on the two bodies.[13] As a tertiary, monacid base strychnine forms with methyl iodide only a monomethiodide, $C_{21}H_{22}N_2O_2 \cdot CH_3I$. If this is now treated with moist silver oxide, there is not obtained, as one might expect, the methyl hydroxide of strychnine,



but this derivative, serving simply as an intermediate product in the reaction passes first into the methyl hydroxide of strychnol and then into the betaïne-like derivative, *methylstrychnine*, $C_{22}H_{26}N_2O_3$:



Methyl hydroxide of strychnine — Methyl hydroxide of strychnol



Methylstrychnine

The constitution of methylstrychnine (*strychnol-methylbetaïne*) follows on the one hand from its secondary basic character (formation of nitrosamine), and on the other from its yielding with hydriodic acid *strychnol methiodide*, $\genfrac{}{}{0pt}{}{I}{CH_3}\rangle N{\equiv}C_{20}H_{22}O\langle\genfrac{}{}{0pt}{}{COOH}{NH}$,

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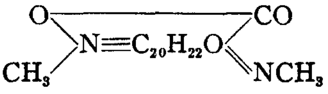
[13] Tafel, A. 264, 33. Monfang and Tafel, A. 304, 49.

and from the reconversion of this iodide into methylstrychnine through the action of silver oxide.

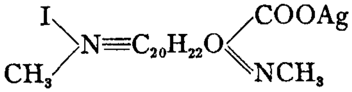
Methylstrychnine, accordingly, appears to be a derivative not of strychnine but of strychnol.

Methylstrychnine can take up a second CH_3 group and forms thus dimethylstrychnine, $C_{23}H_{28}N_2O_3$:

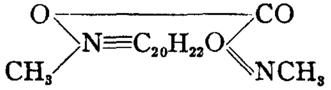


Dimethylstrychnine

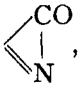
This dimethylstrychnine is also formed by heating the silver salt of methylstrychnol methiodide:



Methylstrychnol methiodide



Dimethylstrychnine

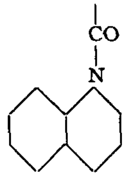
Dimethylstrychnine is thus *methylstrychnol-methylbetaïne.* This derivative possesses the character of a tertiary base and in its entire behavior, particularly towards benzaldehyde and nitrous acid and in the formation of dyestuffs, shows the closest resemblance to the dialkylated anilines, especially to nitrogen-methyltetrahydroquinoline. From this Tafel concludes that the triatomic nitrogen of dimethylstrychnine, viz., the non-basic nitrogen of strychnine in the group , is directly attached to an aromatic ring in the form of a quinoline nucleus.

The presence of a quinoline ring in the molecule of strychnine is also indicated in the behavior of the alkaloid toward nitric acid.

There is thus formed in addition to picric acid [14] a monobasic acid, *dinitrostrychol carboxylic acid,* $C_9H_2N(NO_2)_2(OH)_2COOH$. When the latter is heated with water to 200°, it loses carbon

[14] Shenstone, Soc. 47, 139. Tafel, B. 26, 333.

dioxide and yields *dinitrostrychol*, $C_9H_3N(NO_2)_2(OH)_2$, which Tafel regards as a *dinitrodioxyquinoline*. According to this view strychnine contains a quinoline ring, and we may assume that there is present the following grouping:



By the action of dilute nitric acid on strychnine, there is formed furthermore a substitution-product, *cacostrychnine*.[15] The presence of a quinoline nucleus in the strychnine molecule is also indicated in another series of derivatives.

On heating strychnine with baryta-water to 140°, Gal and Etard[16] obtained two bodies of the formulæ $C_{21}H_{26}N_2O_4$ and $C_{21}H_{28}N_2O_5$, which they named *dihydrostrychnine* and *trihydrostrychnine*. Tafel, who investigated the first compound more thoroughly, showed that its composition must be represented by $C_{21}H_{24}N_2O_3+H_2O$. It is thus an isomer of strychninic acid and may be designated as *isostrychninic acid*. In all its behavior isostrychninic acid appears to be most closely related to strychninic acid. Like the latter it contains a carboxyl and an imide group, and on methylation forms methylisostrychninic acid,

$$N{\equiv}C_{20}H_{22}O\begin{cases}COOH \\ NCH_3\end{cases};$$

isomethylstrychnine,

$$\begin{matrix}O \\ CH_3\end{matrix}\!\!>\!N{\equiv}C_{20}H_{22}O\begin{cases}CO \\ NH\end{cases};$$

and isodimethylstrychnine,

$$\begin{matrix}O \\ CH_3\end{matrix}\!\!>\!N{\equiv}C_{20}H_{22}O\begin{cases}CO \\ NCH_3\end{cases}.$$

(In the last two formulæ a line joins the O to the CO.)

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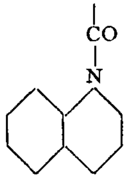
[15] Claus and Glassner, B. 14, 773. Tafel, A. 301, 336.
[16] Gal and Etard, Bl. [2] 31, 98.

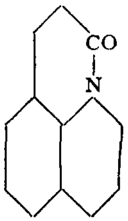
All these alkylated iso-derivatives behave toward benzaldehyde and nitrous acid and in the formation of dyes, etc., as does tetrahydroquinoline.

It has, however, as yet been found impossible to convert strychnine into known quinoline derivatives.

According to Tafel's view the tetrahydroquinoline ring in the molecule of strychnine is united further with a piperidone nucleus, since the CO group in the complex,



must be again joined to the quinoline nucleus to form a ring, possibly in the following way:



Otherwise in the transformation of strychnine to strychnol the entire complex of the strychnine molecule would probably not remain intact.

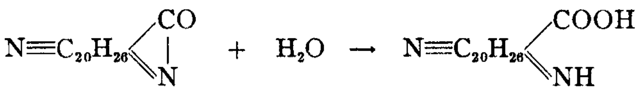
The reduction of strychnine has led to a series of derivatives which in their general behavior in many ways resemble tetrahydroquinoline.

By heating strychnine with hydriodic acid and phosphorus, Tafel succeeded in eliminating one of the atoms of oxygen and in obtaining the reduction-product, *desoxystrychnine*, $C_{21}H_{26}N_2O$:

$$\underset{\text{Strychnine}}{C_{21}H_{22}N_2O_2} + 6H \rightarrow \underset{\text{Desoxystrychnine}}{C_{21}H_{26}N_2O} + H_2O.$$

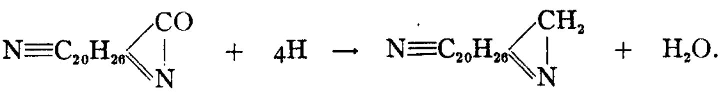
Desoxystrychnine crystallizes with three molecules of water; the anhydrous derivative melts at 172°, distils without decomposition, and in its toxic action closely resembles strychnine; it is a monacid, tertiary base, in optical activity, lævorotatory.

The oxygen atom, which has been eliminated, comes not from the carbonyl, but from the group $NC_{20}H_{22}O$, since desoxystrychnine, on being heated with sodium alcoholate to 180°, is converted into *desoxystrychninic acid*—a reaction which is analogous to that in which strychninic acid is formed:



Desoxystrychnine — Desoxystrychninic acid

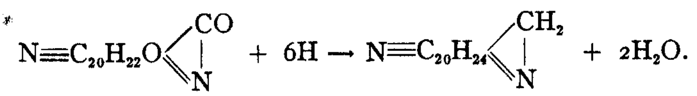
By electrolytic reduction in sulphuric acid solution the second oxygen atom may be removed from desoxystrychnine and there results *dihydrostrychnoline*, $C_{21}H_{28}N_2$:



Desoxystrychnine — Dihydrostrychnoline

Dihydrostrychnoline forms prisms melting at 129°; it boils at 267–270°; it is dextrorotatory and is not a tetanic poison.

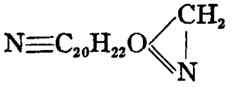
If strychnine is reduced with hydriodic acid and phosphorus and subsequently with sodium and amyl alcohol, it is converted into *strychnoline*, $C_{21}H_{26}N_2$ (crystals melting at 175–178°; not a tetanic poison):



Strychnine — Strychnoline

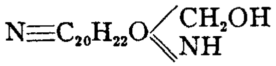
Electrolytic reduction of strychnine gives rise to two bases, *tetrahydrostrychnine*, $C_{21}H_{26}N_2O_2$, and *strychnidine*, $C_{21}H_{24}N_2O$,

the latter of which is derived from the former by loss of water.[17] Strychnidine (a diacid base, crystallizes in needles, melting-point 256.6°) in all its behavior most closely resembles dihydrostrychnoline; it may consequently be represented by the following formula:



Strychnidine

Tetrahydrostrychnine (diacid, secondary base, melting-point 202°) must then be represented as follows:



Tetrahydrostrychnine

The second oxygen atom in the strychnine molecule has been the subject of considerable study, but as yet little is known regarding its function. It is not present in an oxymethyl group (hydrochloric acid does not split off methyl chloride) nor in a hydroxyl (it is unaffected by acetic anhydride).

Tafel[18] believes that we have here an ether grouping and this view is not improbably correct. Minunni and Ortoleva,[19] however, suspect the presence of a hydroxyl. A benzoyl derivative of strychnine, which is mentioned by Schützenberger[20] and which would point to the existence of a hydroxyl group, needs to be investigated more fully.

Despite the data which have been accumulated, our knowledge of the constitution of strychnine is, as we see, very incomplete. We can at best only infer that the nucleus of the molecule comprises a complex ring system.

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[17] Tafel, A. 301, 291; Ber. 33, 2216.
[18] Tafel, A. 301, 293.
[19] Minunni and Ortoleva, G. 30, I, 39.
[20] Schützenberger, C. r. 47, 233.

2. Brucine.

Brucine was isolated in 1819 by Pelletier and Caventou[21] from "false Angustura-bark." It possesses the formula $C_{23}H_{26}N_2O_4$, and crystallizes in prisms which ordinarily contain four molecules of water; crystals with two molecules of water have, however, been observed. The anhydrous alkaloid melts at 178°. Brucine is very similar to strychnine; like the latter, it is a monacid, tertiary, lævorotatory base. Its physiological action is the same, though somewhat more feeble. Its solubility in water and alcohol is slightly greater than that of strychnine.

Brucine contains two methoxyl groups.[22] When the alkaloid is heated with hydrochloric acid to 140°, one molecule of methyl chloride is eliminated and there is formed a phenol-like derivative which melts at 284° and which may be reconverted into brucine by the action of methyl iodide and caustic potash.[23] The prolonged action of hydrochloric acid on brucine effects the elimination of two molecules of methyl chloride.

The halogens with brucine form substitution-products; nitric acid yields nitro-derivatives, but at the same time acts as an oxidizing and saponifying agent.[24]

Manganese dioxide, mercuric oxide, and chromic acid oxidize the alkaloid with the formation of methyl alcohol, formic acid, and carbon dioxide.[25]

Electrolytic reduction changes brucine to *tetrahydrobrucine*, $C_{23}H_{30}O_4N_2$ (melting-point 208–209°).[26] When this derivative is heated slightly above its melting-point (215–220°) it loses water and forms *brucidine*, $C_{23}H_{28}O_3N_2$ (needles, melting-point *in vacuo* 198°).

[21] Pelletier and Caventou, A. ch. [2] 12, 113; 26, 53.
[22] Zeisel, M. 6, 989. Shenstone, Soc. 43, 101.
[23] Hanssen, B. 17, 2266.
[24] Strecker, A. 91, 76.
[25] Baumert, A. 70, 330.
[26] Tafel, A. 304, 24; Ber. 34, 3291.

Boiling with caustic soda converts brucine into *hydrobrucine*, $C_{23}H_{28}N_2O_5$; this hydrobrucine, however, appears to be the analogue of strychninic acid and is consequently named by Monfang and Tafel[27] *brucinic acid:*

$$N{\equiv}C_{20}H_{20}(OCH_3)_2O{<}\begin{matrix}COOH\\NH\end{matrix}$$

Brucinic acid

On fusing brucine with caustic potash, Oechsner[28] noted the following pyridine bases, which under like conditions are also obtained from cinchonine (page 342):

β-Lutidine (β-ethylpyridine).
α-Collidine ($\alpha\alpha'$-methyl-ethylpyridine).
β-Collidine (β-ethyl-γ-methylpyridine).

According to Loebisch and Schoop,[29] brucine yields carbazol on distillation over zinc-dust. Heated with lime it forms such decomposition-products as ammonia, methylamine, β-picoline, β-lutidine, and traces of skatol.[30]

Brucine appears to be the dimethoxy-derivative of strychnine. In strict correspondence with the existence in brucine of two methoxyl groups and with their absence in strychnine is the difference, $C_2H_4O_2$, between the molecular weights of the two alkaloids. Their similarity in behavior indicates that the two bases are closely allied.

The above relation between the two alkaloids appears to be confirmed by an observation of Hanssen.[31] By the oxidation of strychnine and brucine with chromic acid he obtained the same monobasic acid, $C_{15}H_{17}N_2O_2 \cdot COOH$ (melting-point 263–264°).

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[27] Monfang and Tafel, A. 304, 24.
[28] Oechsner, C. r. 95, 298; 99, 1077.
[29] Loebisch and Schoop, M. 7, 609.
[30] Stoehr, J. pr. 42, 415.
[31] Hanssen, B. 17, 2849; 18, 777, 1917; 20, 451.

Brucine and strychnine, accordingly, contain the same group, $C_{15}H_{17}N_2O_2$, and differ only in that part of the molecule, which oxidation converts into a carboxyl group. This second part contains the two methoxyls of brucine, since they are not found in the oxidation-product. We may then formulate the constitutions of the two alkaloids as follows:

$$\underset{\text{Strychnine}}{C_{15}H_{17}N_2O_2{-}C_6H_5}; \qquad \underset{\text{Brucine}}{C_{15}H_{17}N_2O_2{-}C_6H_3(OCH_3)_2}.$$

It may be noted in passing that the yield of the acid in question, $C_{15}H_{17}N_2O_2(COOH)$, is very small—a fact that slightly diminishes the value of Hanssen's evidence.

3. Strychnicine.

Boorsma [32] recently describes under this name a new alkaloid which he claims to have extracted from the leaves of *Strychnos Nux-vomica*.

Strychnicine crystallizes in anhydrous needles which darken without melting at about 240°. The free alkaloid is tasteless, but its soluble salts are bitter. The toxicity of strychnicine is comparatively slight.

4. Curare Alkaloids.

Roulin and Boussingault [33] in 1830 obtained from curare a crystalline, very poisonous alkaloid, which they named *curarine*. A lack of agreement in the formulæ proposed for the substance [34] received no explanation until the investigations of Boehm [35] showed that curare contains not one but a number of poisonous alkaloids.

Boehm studied three sorts of curare. These may be desig-

[32] Boorsma, *Bulletin de l'Institut botanique de Buitenzorg*, No. **14**, 39.
[33] Roulin and Boussingault, A. ch. [2] **39**, 24.
[34] Preyer, C. r. **60**, 1346. Sachs, A. **191**, 254.
[35] Boehm, A. Pharm. **235**, 660.

nated, according to the mode in which they are originally packed for transportation, as

Tube-curare (packed in bamboo tubes);

Calabash-curare (packed in bottle-gourds);

Pot-curare (packed in small pots of unburnt clay).

Tube-curare, of unknown botanical origin, is the only one of the three on the market. It contains two alkaloids, *tubocurarine* and *curine*.

Tubocurarine, $C_{19}H_{21}NO_4$, forms a reddish-brown, loose powder. It contains a methoxyl group, possesses the character of a quaternary base, and is bitter in taste. Curine, $C_{18}H_{19}NO_3$, crystallizes in colorless, lustrous prisms. Its melting-point is 212°. It is a tertiary base, contains a methoxyl group, and in sulphuric acid solution is lævorotatory. Fusion with potassium hydroxide gives rise to amine bases; distillation with zinc-dust produces probably quinoline derivatives. Curine is at first sweet to the taste, but later bitter.

Calabash-curare is derived from *Strychnos toxifera*. It contains curarine, $C_{19}H_{26}N_2O$, an amorphous, intensely bitter alkaloid.

Pot-curare comes from *Strychnos castelnaca* and contains three alkaloids, *protocurine*, *protocuridine*, and *protocurarine*.

Protocurine, $C_{20}H_{23}NO_3$, forms lustrous needles which melt at 306°; it shows weakly the toxic properties of curare. Protocuridine, $C_{19}H_{21}NO_3$, crystallizes in prisms melting at 274–276°; it is not poisonous. Protocurarine, $C_{19}H_{23}NO_2$, is poisonous.

CHAPTER XXIX.

ALKALOIDS FROM PEGANUM HARMALA.

THE seeds of *Peganum harmala* L. (family of the Rutaceæ) contain two principal alkaloids, *harmaline*, $C_{13}H_{14}N_2O$, discovered in 1841 by Goebel,[1] and *harmine*, $C_{13}H_{12}N_2O$, isolated in 1847 by Fritzsche.[2] In addition to these there occurs in small quantity the alkaloid *harmalol*, $C_{12}H_{12}N_2O$.

These bases are found as phosphates in the integuments of the seed. The alkaloidal content of these amounts in weight to about 4%, of which harmaline forms nearly two-thirds and harmine one-third.

These alkaloids have been studied by Fritzsche,[2] by O. Fischer and Täuber,[3] and by Fischer[4] alone.

1. HARMALINE.

Harmaline crystallizes from methyl alcohol in colorless, lustrous plates which melt with decomposition at 238°. It is slightly bitter to the taste. It is almost insoluble in water, difficultly soluble in cold alcohol and ether, and dissolves readily in hot alcohol. It is a monacid, secondary base, optically inactive; its salts are colored yellow; in solution it exhibits a blue fluorescence, similar to that of acridine. Extracts of *Peganum harmala* are frequently used in the Orient for dyeing substances red.

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[1] Goebel, A. **38**, 363.
[2] Fritzsche, A. **64**, 360; **68**, 351; **72**, 306; **88**, 327; **92**, 330.
[3] O. Fischer and Täuber, B. **18**, 400; **22**, 637.
[4] Fischer, B. **30**, 2481; *Prinz Luitpold's Festschrift*, Erlangen, 1901.

Harmaline, $C_{13}H_{14}N_2O$, is a dihydro-derivative of harmine, $C_{13}H_{12}N_2O$. Oxidizing agents such as potassium permanganate convert it into harmine.

As a secondary base harmaline yields a methyl derivative, *methylharmaline* (small, colorless crystals, melting at 162°), and an acetyl derivative, *acetylharmaline* (melting-point 204–205°). Harmaline is an unsaturated body; reduction with sodium and amyl alcohol or with zinc and hydrochloric acid occasions the addition of two hydrogen atoms with the formation of *dihydro-harmaline*, $C_{13}H_{16}N_2O$. This derivative melts at 199° and is likewise a secondary base (benzoyl derivative).

Harmaline contains a methoxyl but no nitrogen-methyl group.[5] When the alkaloid is heated with fuming hydrochloric acid at 140°, methyl chloride is eliminated and there results a hydroxyl derivative, *harmalol*, of the formula $C_{12}H_{12}N_2O$:

$$\underset{\text{Harmaline}}{C_{12}H_{11}N_2(OCH_3)} + HCl \rightarrow \underset{\text{Harmalol}}{C_{12}H_{11}N_2(OH)} + CH_3Cl.$$

Harmalol crystallizes in red needles which melt at 212°. It possesses the properties both of a base and of a phenol. As we have already noted, harmalol is found in small quantity with harmaline and harmine in the seeds of *Peganum harmala.*

In all probability the molecule of harmaline contains a benzol nucleus. With nitric and sulphuric acids the alkaloid gives the characteristic reactions of aromatic derivatives; heated with sulphuric acid it yields a sulphonic acid; with fuming nitric acid it forms a *nitroharmaline*, $C_{13}H_{13}(NO_2)N_2O$, and some *nitroharmine*, which comes from the oxidation of nitroharmaline.

Much more conclusive, however, are the results obtained by boiling harmaline with nitric acid (density 1.48). There is thus formed in connection with some *harminic acid* (page 398), *nitra-nisic acid* (melting-point 188–189°):

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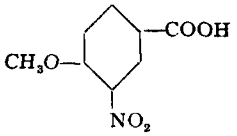
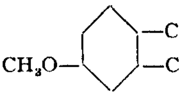
[5] Herzig and Meyer, M. 16, 599.

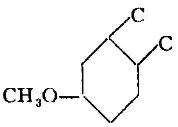


Nitranisic acid

This nitranisic acid is derived apparently from an intermediate product, methoxy-nitrophthalic acid, through the elimination of carbon dioxide. Harmaline must, then, contain a complex of nine carbon atoms, arranged as follows:



or



The relation of the two nitrogen and the remaining four carbon atoms to this grouping is as yet unknown.

2. Harmine.

Harmine separates from its alcoholic solution in prismatic needles; it is little soluble in cold alcohol and ether, almost insoluble in water. Its melting-point is 256–257°. Harmine is optically inactive and may be sublimed. Like harmaline it is a monacid, secondary base.

The salts of harmine are colorless and in aqueous solution give a beautiful, indigo-blue fluorescence. The colorlessness of the salts of harmine in comparison with the yellow color of those of harmaline is somewhat striking, since most colored organic compounds lose their color on reduction.

The conversion of harmine into harmaline has not, as yet, been effected, since reduction of the former leads to the formation of dihydroharmaline, which may consequently be called *tetrahydroharmine.*

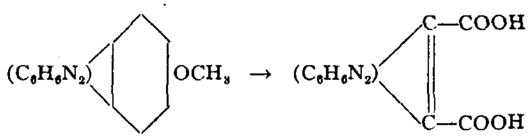
Harmine, like harmaline, is an anisol. Hydrochloric or hydri-

odic acid effects the elimination of methyl halide and thus gives rise to a phenol, *harmol,* $C_{12}H_{10}N_3O$:

$$\underset{\text{Harmine}}{C_{12}H_9N_2(OCH_3)} + HI \rightarrow \underset{\text{Harmol}}{C_{12}H_9N_2(OH)} + CH_3I.$$

Harmol crystallizes in needles which melt at 321°. It dissolves in caustic alkalies and is reprecipitated from its solutions by carbonic acid. On fusion with caustic potash it yields an acid, *harmolic acid,* $C_{12}H_{10}N_2O_6$ (melting-point 246–247°).

The oxidation of harmine or harmol with chromic acid in a solution of glacial acetic acid gives rise to a dibasic acid, *harminic acid,* $C_8H_6N_2(COOH)_2$. In this reaction the methoxyl group and the two carbon atoms have been eliminated and two other carbon atoms have been converted into carboxyl groups. In all probability the formation of harminic acid is brought about through the destruction of the benzol nucleus:



Harmine Harminic acid

This acid crystallizes from hot water in lustrous needles. It melts at 345° and at the same time loses two molecules of carbon dioxide, *apoharmine,* $C_8H_8N_2$, being formed.

The two carboxyls in harminic acid are on neighboring carbon atoms (fluoresceïn formation); it is a secondary derivative (methylharminic acid).

Apoharmine, which melts at 183°, is also a secondary base; its molecular weight corresponds with the above formula. Reduction with hydriodic acid converts the base into *dihydroapoharmine,* $C_8H_{10}N_2$; action with nitric acid gives rise to a nitro-derivitive.

CHAPTER XXX.

ALKALOIDS OF THE ACONITE GROUP.

THE different species of the genus *Aconitum* (family of the Ranunculaceæ) contain a number of alkaloids of which several are as yet somewhat ill-defined. The material afforded by the numerous investigators who have studied these bases is often incomplete, not infrequently contradictory. It is very probable that this has been due in some cases to impure products and in other cases to an application of different names to the same substance.

The investigations of Wright and Luff,[1] which begin in 1875, those of Dunstan and his colaborers,[2] and those of Freund and Beck[3] have done much to dispel this confusion. They have reduced the supposed number of the alkaloids of aconite, have characterized more sharply individual members, and have contributed some interesting matter regarding the constitution of these members.

Nearly every one of the different species of *Aconitum* is characterized by a distinct alkaloid or alkaloids:

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[1] Wright and Luff, Soc. **31**, 146; **33**, 151, 324; **35**, 387; B. **8**, 1466; **9**, 1804; **11**, 349, 1267; **12**, 1215.

[2] Dunstan and Ince, Soc. **59**, 271. Dunstan and Umney, Soc. **61**, 385. Dunstan and Passmore, Soc. **61**, 395. Dunstan and Carr, Soc. **63**, 991; **65**, 176, 290; **67**, 459; B. **27**, 664; **28**, 1379. Chemical News, **72**, 59. Dunstan and Harrisson, Soc. **63**, 443; **65**, 174. Dunstan and Cash, Soc. **68**, 378, 384.

[3] Freund and Beck, B. **27**, 433, 720; **28**, 192, 2537.

Aconitum Napellus contains..............(1) aconitine
and (2) picraconitine.
Aconitum ferox contains..................(3) pseudaconitine.
Aconitum Japonicum contains.............(4) japaconitine.
Aconitum heterophyllum contains..........(5) atisine.
Aconitum Lycoctonum contains............(6) lycaconitine
and (7) mycoctonine.

All these alkaloids of aconite are esters, which on treatment with an alkali or mineral acid undergo hydrolytic dissociation into a base containing hydroxyl and into one or more acids.

In the plant the alkaloids are in combination with aconitic acid, which also occurs in several plants not found in the genus *Aconitum*.

1. ACONITINE.

Aconitine was discovered by Geiger and Hesse[4] in 1833 in the root and leaves of the aconite (*Aconitum Napellus* L.). Under this name it is found on the market, but the product thus obtained does not form a homogeneous substance. Wright and Luff have shown that the amorphous commercial article is a mixture of at least two different bases, for one of which, a crystalline body, they retained the name *aconitine* and to the other, an amorphous substance, they gave the name *picraconitine*.

The composition of aconitine has not been fully established. The two most probable formulæ for the alkaloid are, however, $C_{33}H_{45}NO_{12}$ (Dunstan) and $C_{34}H_{47}NO_{11}$ (Freund and Beck).

Aconitine crystallizes in prisms from a mixture of alcohol and ether. Its melting-point varies somewhat with the rapidity of heating, 189–190° (Dunstan), 197–198° (Freund and Beck). It is almost insoluble in water, readily soluble in benzol, alcohol, and chloroform, more difficultly so in ether. The alcoholic solution is dextrorotatory; aqueous solutions of the hydrochloride

[4] Geiger and Hesse, A. 7. 267.

or hydrobromide are lævorotatory. The taste of aconitine is sharp and bitter. It produces on the tongue a peculiar prickling sensation, strongly irritates the mucous membrane, and is one of the most powerful of the alkaloidal poisons.

It is a tertiary base, in reaction weakly alkaline. It contains four methoxyl and probably three hydroxyl groups.[5]

Halogens act upon aconitine, producing substitution-products.[6]

When the alkaloid is heated by itself, or with water, dilute acids, or alcoholic potash, it suffers a partial decomposition:

1'. On being boiled with a 5% sulphuric acid or, better still, with a saturated solution of tartaric acid, aconitine loses the elements of a molecule of water and yields apoaconitine:

$$\underset{\text{Aconitine}}{C_{33}H_{45}NO_{12}} \rightarrow \underset{\text{Apoaconitine}}{C_{33}H_{43}NO_{11}} + H_2O.$$

Acetic and benzoic anhydrides occasion a similar action, but the elimination is in this case accompanied by the formation of an ester and we obtain a monacetyl- and a monobenzoyl-apoaconitine.

Apoaconitine forms crystals which melt at 186°.5; it is fully as poisonous as aconitine. It possesses only one hydroxyl group and bears accordingly the following relation to aconitine:

$$\underset{\text{Aconitine}}{(C_{33}H_{42}NO_9)\begin{cases} OH \\ OH \\ OH \end{cases}} \qquad \underset{\text{Apoaconitine}}{(C_{33}H_{42}NO_9)\begin{cases} O \\ OH \end{cases}}$$

Dunstan and Passmore state that apoaconitine may be reconverted into aconitine by the absorption of water.

2'. When aconitine is heated with water to 120–130°, or it is treated with alcoholic potash or dilute hydrobromic acid, the molecule is saponified and there are formed *acetic acid* and *picraconitine:*

$$C_{33}H_{45}NO_{12} + H_2O \rightarrow C_{31}H_{43}NO_{11} + C_2H_4O_2,$$

or

$$\underset{\text{Aconitine}}{C_{34}H_{47}NO_{11}} + H_2O \rightarrow \underset{\text{Picraconitine}}{C_{32}H_{45}NO_{10}} + \underset{\text{Acetic acid}}{C_2H_4O_2}.$$

[5] Ehrenberg and Purfürst, J. pr. 45, 604.

[6] Jürgens, J. 1885, 1722.

Aconitine is accordingly the acetic ester of picraconitine:

$$\underset{\text{Aconitine}}{C_{31}H_{39}NO_7(OH)_3(OCOCH_3)}; \qquad \underset{\text{Picraconitine}}{C_{31}H_{39}NO_7(OH)_4}.$$

The regeneration of aconitine from picraconitine by preparing the acetic ester of the latter has not as yet been effected.

On being heated with water to 140–145°, with alkalies, or with mineral acids, picraconitine is also saponified. It is thus decomposed into *benzoic acid* and *aconine:*

$$C_{31}H_{43}NO_{11} + H_2O \rightarrow C_{24}H_{39}NO_{10} + C_7H_6O_2,$$

or

$$\underset{\text{Picraconitine}}{C_{32}H_{45}NO_{10}} + H_2O \rightarrow \underset{\text{Aconine}}{C_{25}H_{41}NO_9} + \underset{\text{Benzoic acid}}{C_7H_6O_2}.$$

Aconitine is consequently *acetyl-benzoylaconine,*

$$C_{25}H_{39}NO_9\left\langle\begin{matrix}COCH_3\\COC_6H_5\end{matrix}\right.$$

On the supposition that this base contains four methoxyl and three hydroxyl groups, the complicated molecule of aconitine may be formulated as follows:

$$\underset{\text{Aconitine}}{C_{21}H_{24}N(OH)_3(OCH_3)_4(OCOCH_3)(OCOC_6H_5)}.$$

3′. According to Dunstan and Carr, when aconitine or its salts are heated above their melting-point, decomposition ensues into *acetic acid* and *pyraconitine:*

$$\underset{\text{Aconitine}}{C_{33}H_{45}NO_{12}} \rightarrow \underset{\text{Pyraconitine}}{C_{31}H_{41}NO_{10}} + \underset{\text{Acetic acid}}{C_2H_4O_2}.$$

This last base forms crystals which melt at 167°.5. It is lævorotatory in acid solution and is non-poisonous. With acetyl chloride it yields a triacetyl derivative.

2. PICRACONITINE.

Picraconitine bears the formula, according to Dunstan, of $C_{31}H_{43}NO_{11}$, according to Freund and Beck, of $C_{32}H_{45}NO_{10}$. This second alkaloid of *Aconitum Napellus* is an amorphous, very bitter, non-poisonous substance; it melts with decomposition at 125°; it is difficultly soluble in water, readily so in alcohol; in neutral solution it is dextro-, in acid lævorotatory.

We have already noted above that in the saponification of aconitine, picraconitine occurs as an intermediate product, which on further action of alcoholic potash is decomposed into benzoic acid and aconine. Picraconitine is consequently the monobenzoic ester of aconine.

It contains four methoxyl and four hydroxyl groups. Acetyl chloride at 100° converts it into a tetracetyl derivative, which is not, however, as one might suspect, identical with triacetyl aconitine.

Aconine, $C_{24}H_{39}NO_{10}$ or $C_{25}H_{41}NO_{9}$.—Aconine forms a resinous, deliquescent mass, readily soluble in water and alcohol, insoluble in ether. It melts at 132°, is extremely bitter, but possesses almost no physiological action. In neutral solution the base is dextrorotatory; in acid, lævorotatory. Fehling's solution or an ammoniacal silver solution is reduced on being boiled with aconine. The base is not affected by nitric acid.

Aconine contains four methoxyl and five hydroxyl groups; with benzoic anhydride, however, it yields only a dibenzoyl and with acetyl chloride only a tetracetyl derivative.

Regarding the structure of the molecule of aconine we know as yet but little. From the oxidizing action of potassium permanganate only oxalic acid appears to have been detected. On distilling the base with barium hydroxide, Ehrenberg and Purfürst obtained, in addition to hydrocarbons of the fatty series, methylamine and a base (boiling-point 237–240°) which appears to be quinoline or tetrahydroquinoline.

In addition to aconitine and picraconitine, there are found in *Aconitum Napellus* several other alkaloids, such as the *aconel-*

line of T. and H. Smith,[7] the *napelline* of Morson,[8] the *acolyctine* of Hübschmann,[9] the *isoaconitine* of Dunstan and Umney. These are, however, probably all identical with one or another of the aconite alkaloids mentioned at the beginning of this chapter.

3. PSEUDACONITINE.

Pseudaconitine is found in *Aconitum ferox* Wall. as a crystalline derivative, together with a little aconitine and a somewhat larger quantity of amorphous bases. It was formerly described in an impure condition under different names by Wiggers, Ludwig, Flückiger, and Hübschmann, but was first isolated as a pure derivative by Wright and Luff[10] in 1878. They gave to it the name pseudaconitine and determined its composition as $C_{36}H_{49}NO_{12}$.

Pseudaconitine crystallizes in prisms containing one molecule of water; in the anhydrous condition it melts at 201° (Dunstan and Carr), 210–212° (Freund and Niederhofheim[11]); it is almost insoluble in water, somewhat difficultly soluble in ether, readily soluble in alcohol and chloroform. It is burning to the taste and is still more poisonous than aconitine; in neutral solution it is dextro-, in acid, lævorotatory. In its behavior it closely resembles aconitine.[12]

When pseudaconitine is heated with water to 135° it is decomposed into *acetic acid* and *picropseudaconitine:*

$$\underset{\text{Pseudaconitine}}{C_{36}H_{49}NO_{12}} + H_2O \rightarrow \underset{\text{Picropseudaconitine}}{C_{34}H_{47}NO_{11}} + \underset{\text{Acetic acid}}{C_2H_4O_2}.$$

Picropseudaconitine crystallizes from ether with one molecule of water; it is lævorotatory, melts at 210°, is almost insoluble

[7] T. and H. Smith, *Pharmaceutical Journal*, [2] 5, 317.
[8] Morson, *Annalen der Physik und Chemie*, 42, 175.
[9] Hübschmann, J. 1857, 416; 1866, 483.
[10] Wright and Luff, Soc. 33, 151, 330.
[11] Freund and Niederhofheim, B. 29, 852.
[12] Dunstan and Carr, *Chemical News*, 72, 59; 84, 27. *Chemiker-Zeitung*, 19, 1373.

in water, readily soluble in alcohol and ether, and is not poisonous.

Under the action of alcoholic soda at 100°, pseudaconitine suffers decomposition into *acetic acid, veratric acid* (page 288), and *pseudaconine:*

$$\underset{\text{Pseudaconitine}}{C_{36}H_{49}NO_{12}} + 2H_2O \rightarrow \underset{\text{Pseudaconine}}{C_{25}H_{39}NO_8} + \underset{\text{Veratric acid}}{C_9H_{10}O_4} + \underset{\text{Acetic acid}}{C_2H_4O_2}.$$

Pseudaconine is a yellow, deliquescent, amorphous substance which melts at 100° and dissolves readily in water, alcohol, and ether. It reduces silver solutions, is strongly alkaline in reaction, contains four methoxyl groups. To the taste it is bitter; in optical activity, dextrorotatory.

The action of dilute mineral acids or of tartaric acid eliminates from pseudaconitine a molecule of water and gives rise thereby to *apopseudaconitine:*

$$\underset{\text{Pseudaconitine}}{C_{36}H_{49}NO_{12}} \rightarrow \underset{\text{Apopseudaconitine}}{C_{36}H_{47}NO_{11}} + H_2O.$$

This crystallizes with one molecule of water in needles which melt at 102–103°. It forms a monacetyl and a monobenzoyl derivative and possesses accordingly one hydroxyl group.

By the action of alcoholic potash at 140°, pseudaconitine (as also apopseudaconitine) is decomposed into acetic acid, veratric acid, and *apopseudaconine:*

$$\underset{\text{Pseudaconitine}}{C_{36}H_{49}NO_{12}} + 2H_2O \rightarrow \underset{\text{Apopseudaconine}}{C_{25}H_{37}NO_7} + \underset{\text{Veratric acid}}{C_9H_{10}O_4} + \underset{\text{Acetic acid}}{C_2H_4O_2} + H_2O.$$

Apopseudaconine is much like pseudaconine; it contains two hydroxyl groups and forms with acetic and benzoic anhydrides diacetyl and dibenzoyl derivatives.

From all these reactions, pseudaconitine appears to be acetylveratrylpseudaconine,

$$\underset{\text{Pseudaconitine}}{C_{21}H_{23}N(OH)_2(OCH_3)_4 \left\langle \begin{matrix} OCOCH_3 \\ OCOC_6H_3(OCH_3)_2 \end{matrix} \right.}$$

Of the structure of pseudaconine little is known. Possibly it may be an anhydro-derivative of aconine (page 403).

4. JAPACONITINE.

Wright and Luff[13] obtained from the root of Japanese aconite (*Aconitum Japonicum* Hort.) an alkaloid which they named *japaconitine* and to which they ascribed the formula $C_{66}H_{88}N_2O_{21}$. This alkaloid is a crystalline body melting at 185–186°; it forms a tetrabenzoyl derivative. Alcoholic potash saponifies the base, giving rise to *benzoic acid* and the amorphous *japaconine* (closely resembles aconine):

$$\underset{\text{Japaconitine}}{C_{66}H_{88}N_2O_{21}} + 3H_2O \rightarrow \underset{\text{Japaconine}}{2C_{26}H_{41}NO_{10}} + \underset{\text{Benzoic acid}}{2C_7H_6O_2}.$$

Mandelin[14] as also Freund and Beck regard japaconitine as identical with aconitine. On the other hand, Dunstan and Read[15] contend for the existence of japaconitine, only they assign to the base a different formula and somewhat different properties from those noted by Wright and Luff.

Their formula for the alkaloid is $C_{34}H_{49}NO_{11}$; melting-point 204°.5. It contains an acetyl, a benzoyl, and four methoxyl groups and yields well-defined salts. The free base is dextro-, the salts lævorotatory. The specific rotatory power of japaconitine is greater than that of aconitine and the difference is said to be sufficiently characteristic to serve as a means of distinguishing the two bases.

On saponification, japaconitine yields first *acetic acid* and *japbenzaconine* (crystals, melting-point 182–183°),

$$\underset{\text{Japaconitine}}{C_{34}H_{49}NO_{11}} + H_2O \rightarrow \underset{\text{Japbenzaconine}}{C_{32}H_{47}NO_{10}} + \underset{\text{Acetic acid}}{C_2H_4O_2},$$

and then the latter is in turn dissociated into *benzoic acid* and *japaconine* (amorphous):

[13] Wright and Luff, Soc. 35, 387.
[14] Mandelin, A. Pharm. 223, 97, 129, 161.
[15] Dunstan and Read, Soc. 77, 45.

$$\underset{\text{Japbenzaconine}}{C_{32}H_{47}NO_{10}} + H_2O \rightarrow \underset{\text{Japaconine}}{C_{25}H_{43}NO_9} + \underset{\text{Benzoic acid}}{C_7H_6O_2}.$$

When japaconitine is melted it yields acetic acid and *pyrojapaconitine*, $C_{32}H_{45}NO_9$ (*apojapbenzaconine*), which like the aconitine derivatives experiences further decomposition into benzoic acid and *pyrojapaconine*, $C_{25}H_{41}NO_8$ (*apojapaconine*) (amorphous).

5. Atisine.

Atisine, $C_{22}H_{31}NO_2$, is found, according to Jowett,[16] in the root of *Aconitum heterophyllum* Wall. It is an amorphous substance, little soluble in water, more readily soluble in organic solvents. It is not poisonous. The free base is lævo-, the salts dextrorotatory.

6. Lycaconitine and 7. Mycoctonine.

Dragendorff and Spohn[17] found in the root of *Aconitum lycoctonum* L. two alkaloids, *lycaconitine*, $C_{27}H_{34}N_2O_6+2H_2O$, and *mycoctonine*, $C_{27}H_{30}N_2O_8+5H_2O$. From the saponification of both these are obtained *lycaconine*, $C_{33}H_{56}N_4O_8$, a crystalline acid, *lycoctonic acid*, $C_{17}H_{18}N_2O_7$, and a *dioxybenzoic acid*.

From the same plant Hübschmann[18] has isolated two alkaloids which he names *acolyctine* and *lycoctonine*. Wright, however, considers that these are identical with aconine and pseudaconine.

Aconitic Acid.

Aconitic acid, which occurs in the plant in combination with all the aconite bases, was isolated by Peschier[19] in 1828. It is a tribasic acid, whose constitution,

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[16] Jowett, Soc. **69**, 1518.

[17] Dragendorff and Spohn, *Pharmaceutische Zeitschrift für Russland*, **23**, 313.

[18] Hübschmann, J. 1866, 483.

[19] Peschier, *Trommsdorf's Journal der Pharmacie*, **5**, 1, 93; **8**, 1, 266.

$CH_2—COOH$
|
C—COOH
‖
CH—COOH
Aconitic acid

is established by the following reactions:[20]

1′. When heated to its melting-point (187–188°), aconitic acid is decomposed into carbon dioxide and *itaconic anhydride.*

2′. Reduction with sodium amalgam gives rise to *tricarballylic acid.*

3′. Aconitic acid reacts with one molecule of hydrogen bromide to form *bromtricarballylic acid,* $C_6H_7BrO_6$, and with three atoms of bromine to form *tribromtricarballylic acid.*[21]

4′. With hypochlorous acid it yields *chlorcitric acid.*

5′. Finally by heating citric acid alone, or with concentrated hydrochloric or sulphuric acid, water is eliminated and aconitic acid is obtained.

The relation of aconitic acid to itaconic, tricarballylic, and citric acids is clearly set forth in the following formulæ:

$CH_2—COOH$	$CH_2—COOH$	$CH_2—COOH$	$CH_2—COOH$
|	|	|	|
C—COOH	CH—COOH	C(OH)—COOH	C—COOH
‖	|	|	‖
CH_2	$CH_2—COOH$	$CH_2—COOH$	CH—COOH
Itaconic acid	Tricarballylic acid	Citric acid	Aconitic acid

Later syntheses of aconitic acid fully substantiate the correctness of the above formula for the acid.[22]

One of these (Claisen and Hori) is of considerable interest, since it starts with the esters of oxalic and acetic acids and thus indicates the possible origin of aconitic acid in the plant.

[20] Crasso, A. **34**, 56. Dessaignes, C. r. **31**, 342; **42**, 494, 524; **55**, 510. Dahlström, J. pr. **14**, 355.

[21] Guinochet, C. r. **108**, 300.

[22] Loven, B. **22**, 3053. Buchner, B. **22**, 2929. Claisen and Hori, B. **24**, 120. Conrad, B. **32**, 1005.

CHAPTER XXXI.

THE VERATRUM ALKALOIDS.

Of the numerous species of the genus *Veratrum*, two members, *Veratrum Sabadilla* and *Veratrum album*, are noteworthy on account of their alkaloidal content.

A. Alkaloids of the Cevadilla.

Veratrine, the active principle of the seeds of the cevadilla (*Veratrum Sabadilla* Retz. or *Sabadilla officianalis* Brandt, family of the Liliaceæ), was isolated by Meissner [1] in 1818. This commercial veratrine is a white, amorphous powder, which melts at about 150°. It is not, however, a homogeneous substance, but as has been shown by the investigations of Schmidt and Köppen,[2] Wright and Luff,[3] and Bosetti,[4] it is a mixture which contains at least three different well-defined alkaloids:

Crystalline veratrine (cevadine) ..... $C_{32}H_{49}NO_9$.
Veratridine (amorphous veratrine) ... $C_{37}H_{53}NO_{11}$.
Sabadilline (cevadilline)........... $C_{34}H_{53}NO_8$.

To these may be added two other alkaloids more recently discovered by Merck,[5] viz., *sabadine*, $C_{29}H_{51}NO_8$, and *sabadinine*, $C_{27}H_{45}NO_8$. These bases have as yet been only incompletely investigated.[6]

[1] Meissner, *Schweiggers Journal für Chemie und Physik*, **25**, 377.
[2] Schmidt and Köppen, B. **9**, 1115.
[3] Wright and Luff, Soc. **33**, 338.
[4] Bosetti, A. Pharm. **221**, 81.
[5] Merck, A. Pharm. **229**, 164.
[6] Allen, *Pharmaceutical Journal*, 1896, 146.

From 10 kg. of the seed of the cevadilla, Wright and Luff obtained 60–70 g. of basic derivatives and from this 8–9 g. of pure crystalline veratrine, 5–6 g. veratridine, and 2–3 g. of cevadilline.

The alkaloids are in the plant in combination with *cevadic* and *veratric acids*, the former of which is very probably identical with *tiglic acid.*[7]

1. CRYSTALLINE VERATRINE.

Veratrine, $C_{32}H_{49}NO_9$, has been studied chiefly by Merck,[8] Bosetti, Ahrens, Wright and Luff, of whom the last designate the base under the name of *cevadine.* It crystallizes from alcohol with one molecule of the solvent in needles, which after being dried melt at 205°.[9] It is insoluble in hot water and alkalies, little soluble in ether, readily soluble in alcohol. It is optically inactive.[10]

Veratrine possesses a sharp and burning taste; it is odorless, but on being brought in contact with the mucous membrane of the nose it provokes violent sneezing. It is a powerful emetic and in larger doses one of the most active tetanic poisons.

Cevadine is a tertiary base; it contains no methoxyl and no nitrogen-methyl group; it forms addition-products with two and four atoms of bromine; at the same time the bromine to a slight extent effects substitution.[11] Alcoholic potash decomposes cevadine into *cevine* and *tiglic acid* (methylcrotonic acid):

$$\underset{\text{Veratrine}}{C_{32}H_{49}NO_9} + H_2O \rightarrow \underset{\text{Cevine}}{C_{27}H_{43}NO_8} + \underset{\text{Tiglic acid}}{C_5H_8O_2}.$$

Cevine, $C_{27}H_{43}NO_8$, crystallizes with three and one-half molecules of water; on being heated it is converted into a trans-

[7] Pelletier and Caventou, A. ch. [2] 14, 69.
[8] Merck, A. 95, 200.
[9] Freund and Schwarz, B. 32, 800.
[10] Buignet, J. 1861, 49.
[11] Ahrens, B. 23, 2700.

parent resin; it dissolves in dilute acids and in an excess of caustic alkali, with which it forms salts. Cevine is less poisonous than cevadine.

Bosetti, Ahrens, and Stransky[12] have also noted the ready saponification of veratrine by the action of alkalies (caustic potash, ammonia, barium hydroxide) and even by the action of water alone at 200°, but they found that the acid decomposition-product is *angelic acid* and that in the process of isolating this it is converted into its isomer, tiglic acid. Freund and Schwarz in the decomposition of veratrine observed a mixture of both these acids.

When veratrine is oxidized with chromic acid, acetaldehyde is formed, while potassium permanganate gives rise to acetic and oxalic acids.

By dry distillation of cevadine, Ahrens states that he obtained tiglic acid and β-picoline. When the alkaloid is heated with lime, there are formed, according to the same investigator, β-picoline, β-pipecoline, and an unsaturated hydrocarbon, C_4H_8, which he regards as isobutylene, $(CH_3)_2{=}C{=}CH_2$, but which from the constitution of tiglic acid should be symmetrical butylene, $CH_3{-}CH{=}CH{-}CH_3$.

Angelic and Tiglic Acids.—These two acids, which are found in a large number of plants, are stereoisomers and possess the formula $C_5H_8O_2$.

Angelic acid crystallizes in prisms melting at 45.5°; it boils at 185°. On being kept for some time at its boiling temperature, it is converted into tiglic acid. Concentrated sulphuric acid at 100° effects the same change.

Tiglic acid forms tabular crystals which melt at 64.5°; it boils at 198.5°.

The constitution of both these acids, $CH_3{-}CH{=}C\begin{cases}CH_3\\COOH\end{cases}$, is determined from the following reactions:

1′. Both acids add bromine to form the same *dibromvaleric acid*,

[12] Stransky, M. 11, 482.

$$CH_3—CHBr—CBr\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right. ,$$

and with hydrogen bromide yield the same ***bromvaleric acid***,[13]

$$CH_3—CH_2—CBr\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right.$$

2′. Reduction converts both acids into the same valeric acid:[14]

$$CH_3—CH_2—CH\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right.$$

3′. Tiglic ester is formed by the action of phosphorus trichloride on *methyl-ethyl-oxyacetic ester:*[15]

$$CH_3—CH_2—C(OH)\left\langle\begin{matrix}CH_3\\COOC_2H_5\end{matrix}\right.$$

4′. Tiglic acid results further from the distillation of *α-methyl-β-oxybutyric acid:*[16]

$$CH_3—CH(OH)—CH\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right.$$

These facts do not permit us to present two *different* constitutional formulæ for these isomeric acids. Both acids are to be regarded as *α-methylcrotonic acid*, $CH_3—CH{=}C\left\langle\begin{matrix}CH_3\\COOH\end{matrix}\right.$. Their stereoisomerism is of the same sort as that in *maleïc and fumaric acids.*

From these as yet incomplete data the constitution of veratrine may be formulated as follows:

$$C_{27}H_{42}NO_7—O—CO—C\left\langle\begin{matrix}CH_3\\CH—CH_3\end{matrix}\right.$$

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[13] Pagenstecher, A. **195**, 109.

[14] Schmidt and Berendes, A. **191**, 94.

[15] Frankland and Duppa, Soc. [2] **3**, 133. A. **136**, 9.

[16] Rohrbeck, A. **188**, 235.

2. VERATRIDINE.

Veratridine, $C_{37}H_{53}NO_{11}$,[17] was isolated by Schmidt and Köppen[18] in 1876. It is an amorphous substance, somewhat soluble in water and melting at 180°. When boiled with alcoholic soda it is saponified, yielding *verine* and *veratric acid:*

$$\underset{\text{Veratridine}}{C_{37}H_{53}NO_{11}} + H_2O \rightarrow \underset{\text{Verine}}{C_{28}H_{45}NO_8} + \underset{\text{Veratric acid}}{C_9H_{10}O_4}.$$

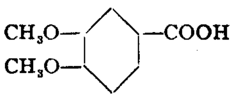
Verine forms a yellow, amorphous derivative which melts at 130°. It resembles cevine, of which, according to Wright and Luff, it is a higher homologue; possibly, however, the two bases are identical.

Veratric Acid, $C_9H_{10}O_4$.—This acid results not only from the decomposition of veratridine, but also from that of several other alkaloids (papaverine, berberine, pseudaconitine).

The acid is found in small quantity in the seeds of the cevadilla, where it was discovered by E. Merck[19] in 1839.

It is somewhat soluble in hot water, but is precipitated almost completely when the solution is cooled. It crystallizes in prisms containing a molecule of water and melts at 181°. The acid is quite soluble in alcohol and ether.

Veratric acid is the dimethyl ether of protocatechuic acid (3,4-*dimethoxybenzoic acid*):



This constitution is established by the following three reactions:

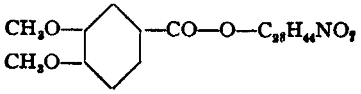
1'. Fusion with caustic potash or treatment with hydriodic acid at 160° converts veratric acid into protocatechuic acid.[20]

[17] Wright and Luff, Soc. **33**, 353.
[18] Schmidt and Köppen, B. **9**, 1115.
[19] E. Merck, A. **29**, 188.
[20] Körner, B. **9**, 582.

2′. Distillation with barium oxide gives rise to dimethylpyrocatechin (veratrol).[21]

3′. Veratric acid is formed by treating protocatechuic acid or its monomethyl ethers (vanillic and isovanillic acids) with methyl iodide and caustic potash.[22]

Veratridine is accordingly *veratrylverine:*



3. SABADILLINE.

This base was obtained from commercial veratrine by Couerbe[23] in 1834.

According to Couerbe, sabadilline possesses the formula $C_{21}H_{27}N_2O_7$; it crystallizes from benzol in needles or in leaflets which are insoluble in ether, but are readily soluble in alcohol and hot water. It is said that the base does not provoke sneezing nor does it act as an emetic.

Wright and Luff describe, under the name of cevadilline, an alkaloid which they regard as identical with the sabadilline of Couerbe, although they could not obtain it crystallized and assigned to it a quite different formula, $C_{34}H_{53}NO_8$. By the action of caustic potash they succeeded in decomposing it into *tiglic acid* and *cevilline:*

$$\underset{\text{Cevadilline}}{C_{34}H_{53}NO_8} + H_2O \rightarrow \underset{\text{Cevilline}}{C_{29}H_{47}NO_7} + \underset{\text{Tiglic acid}}{C_5H_8O_2}.$$

B. ALKALOIDS OF THE WHITE HELLEBORE.

The roots of the European hellebore (*Veratrum album* L.) and of related species (*Veratrum viride* Ait. and *Veratrum lobelianum* Bernh.) contain, in addition to a small quantity of vera-

[21] Merck, A. 108, 60.
[22] Kölle, A. 159, 241.
[23] Couerbe, A. ch. [2] 52, 352.

trine,[24] several alkaloids, among which the following five appear to be fairly well characterized:

Jervine	$C_{26}H_{37}NO_3$.
Rubijervine	$C_{26}H_{43}NO_2$.
Pseudojervine	$C_{29}H_{43}NO_7$.
Protoveratrine	$C_{32}H_{51}NO_{11}$.
Protoveratridine	$C_{26}H_{45}NO_8$.

In the plant these bases are in combination with an acid which Pelletier and Caventou regarded as gallic acid, but which Weppen [25] looked upon as a new acid. Weppen gave to it the name *jervic acid* and the formula $C_{14}H_{10}O_{12}+2H_2O$. Schmidt,[26] however, considers this acid to be identical with chelidonic acid (page 21).

1. JERVINE.

Jervine was discovered by Simon [27] in 1837. It crystallizes from alcohol in prisms, whose composition is represented by the formula $C_{26}H_{37}NO_3+2H_2O$. At 100° it loses its water of crystallization and then melts at 238–242°.[28]

Jervine is almost insoluble in water, little soluble in ether, but more soluble in alcohol. It is a weak poison and is not decomposed by alcoholic potash.

2. RUBIJERVINE.

This base forms crystals which melt at 237° (Wright and Luff),[29] 240–246° (Salzberger). It is not poisonous.

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[24] Pelletier and Caventou, A. ch. [2] **14**, 69.
[25] Weppen, A. Pharm. **202**, 101, 193.
[26] Schmidt, A. Pharm. **224**, 513.
[27] Simon, A. ch. [2] **24**, 214.
[28] Salzberger, A. Pharm. **228**, 462. B. **23**, Ref. 699.
[29] Wright and Luff, Soc. **35**, 405.

3. Pseudojervine.

Crystals of this alkaloid melt at 300–307°, are little soluble in alcohol, almost insoluble in ether. Pseudojervine is not poisonous and is not affected by alcoholic potash.

4. Protoveratrine.

Protoveratrine crystallizes in small plates which melt at 245–250° and are difficultly soluble in almost all solvents; its best solvents are chloroform and hot alcohol. It provokes sneezing and is very poisonous.

5. Protoveratridine.

This alkaloid forms crystals which melt at 265°; it is only soluble in chloroform and alcohol; it is not poisonous.

CHAPTER XXXII.

COLCHICINE.

IN 1819 Pelletier and Caventou[1] obtained from the meadow-saffron (*Colchicum autumnale* L. family of the Liliaceæ) a substance of basic properties which they regarded as veratrine. Geiger and Hesse,[2] however, who undertook the study of this body in 1833, recognized in it a new alkaloid, to which they gave the name *colchicine.* But later investigations soon showed that the product of Geiger and Hesse was not a homogeneous substance, and it was not until 1864 that the alkaloid of the meadow-saffron was isolated by Hübler[3] in a condition of purity. Since then colchicine has been studied chiefly by Hertel,[4] Bender,[5] and Zeisel.[6]

The free alkaloid probably exists in all parts of the plant, but principally in the bulbs (0.2%) and in the seeds (0.4%).

According to the investigations of Zeisel, colchicine possesses the formula $C_{22}H_{25}NO_6$; Hübler had previously ascribed to it the composition $C_{17}H_{19}NO_5$, and Hertel and Bender $C_{17}H_{23}NO_6$.

It forms an amorphous, pale-yellow, resinous mass which melts at 145°. It is scarcely soluble in ether, but dissolves readily in water and alcohol; in reaction it is neutral; its aqueous solution is lævorotatory. It is bitter in taste; in small doses it acts as a purgative and an emetic. In general its action resembles that of veratrine, although it does not provoke sneezing on being brought

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[1] Pelletier and Caventou, A. ch. [2] 14, 69.

[2] Geiger and Hesse, A. 7, 274.

[3] Hübler, A. Pharm. [2] 121, 193.

[4] Hertel, *Pharmaceutische Zeitschrift für Russland*, 20, 299.

[5] Bender, *Pharmaceutische Centralhalle*, 26, 291.

[6] Zeisel, M. 4, 162; 7, 557; 8, 870; 9, 1, 865.

in contact with the mucous membrane of the nasal passages. Under the name of *colchisal*, colchicine salicylate is employed somewhat in cases of gout.[7]

Mineral acids at the ordinary temperature convert colchicine into a crystalline substance. Oberlin,[8] who first noted this change, gave the name *colchiceïne* to the reaction-product. Zeisel observed later that in the reaction there is also formed methyl alcohol, so that the conversion of colchicine into colchiceïne is to be represented by the following equation:

$$\underset{\text{Colchicine}}{C_{22}H_{25}NO_6} + H_2O \rightarrow \underset{\text{Colchiceïne}}{C_{21}H_{23}NO_6} + CH_3OH.$$

Zeisel succeeded further in synthesizing colchicine from colchiceïne by heating the latter with methyl iodide in the presence of sodium methylate; the same reaction is brought about more simply by saturating a solution of colchiceïne in methyl alcohol with hydrogen chloride. From this he concluded that colchiceïne is a monobasic acid and that colchicine is its methyl ester:

Colchiceïne.............. $C_{20}H_{22}NO_4(COOH)$.
Colchicine.............. $C_{20}H_{22}NO_4(COOCH_3)$.

This view found confirmation in the fact that colchicine, heated with alcoholic ammonia at 100°, yields an amide, $C_{20}H_{22}NO_4(CONH_2)$, which is decomposed by alcoholic potash into ammonia and colchiceïne.

Colchiceïne forms prismatic needles which contain one-half molecule of water of crystallization; it melts in the hydrous condition at 140°, in the anhydrous at 172°. It is very slightly soluble in water, readily soluble in alcohol, but insoluble in ether. It is also soluble in the alkalies and alkali carbonates and with acids it forms a yellow solution. Its solutions are lævorotatory and of neutral reaction. Colchiceïne does not appear to be poisonous.

[7] Merck, *Merck's Jahresbericht* 1897.
[8] Oberlin, A. ch. [3] 50, 108.

Zeisel has been able to make clear the following points regarding its constitution:

Colchiceïne contains three methoxyl and one acetyl group. Heated with hydrochloric acid, it first loses the latter as acetic acid and then the three methyl groups as methyl chloride. We thus obtain in succession:

Trimethylcolchicinic acid, $C_{15}H_{11}N(OCH_3)_3(COOH)$ (needles, melting-point 159°);

Dimethylcolchicinic acid, $C_{15}H_{11}N(OCH_3)_2(OH)(COOH)$ (prisms, melting-point 141–142°);

Colchicinic acid, $C_{15}H_{11}N(OH)_3(COOH)$ (brown flakes).

The ready elimination of the acetyl group from colchiceïne indicates that this group is not attached to a carbon atom. The attachment can, furthermore, not be to an oxygen atom, since all these are already functionating in methoxyl or carboxyl groups. The acetyl group must, accordingly, be bound to the nitrogen atom; this also follows from the fact that, when trimethylcolchicinic acid is heated with acetic anhydride to 100°, colchiceïne is again formed.

Colchiceïne may then be formulated as follows:

$$C_{15}H_{10}(NCOCH_3)(OCH_3)_3(COOH).$$
Colchiceïne

To the nitrogen atom of colchiceïne, furthermore, there is attached not only an acetyl group, but also a hydrogen atom. There is accordingly present the group $—NH(COCH_3)$. When colchiceïne is treated with methyl iodide, the chief product of the reaction, as we have shown above, is colchicine, but by the action of two molecules of the alkyl halide there is formed at the same time a small quantity of a homologous body, *methylcolchicine,* $C_{23}H_{27}NO_6$. This derivative, which like colchicine is amorphous, is decomposed by hydrochloric acid at 165° with the elimination of acetic acid, methyl chloride, and methylamine. The second methyl group introduced into the molecule of colchiceïne has, accordingly, taken the place of a hydrogen atom, which was attached to the nitrogen.

From these observations we derive the following formulæ:

Trimethylcolchicinic acid	$C_{15}H_9(NH_2)(OCH_3)_3(COOH)$.
Colchiceïne.	$C_{15}H_9(NHCOCH_3)(OCH_3)_3(COOH)$.
Colchicine.	$C_{15}H_9(NHCOCH_3)(OCH_3)_3(COOCH_3)$.

It is evident from these formulæ that there can be no pyridine nor similar nucleus in the molecule of colchicine.

CHAPTER XXXIII.

THE XANTHINE GROUP.

We include under this title a series of seven alkaloids which are closely related to one another in constitution. These seven are:

Xanthine	$C_5H_4N_4O_2$.
Caffeïne	$C_8H_{10}N_4O_2$.
Theobromine	$C_7H_8N_4O_2$.
Theophylline	$C_7H_8N_4O_2$.
Hypoxanthine	$C_5H_4N_4O$.
Guanine	$C_5H_5N_5O$.
Adenine	$C_5H_5N_5$.

These bases form the physiologically active principle of a number of vegetable products which are to-day in quite general use as stimulants, such as tea, coffee, cocoa, Paraguay tea, guarana, and cola-nuts.

Tea-leaves contain all these alkaloids except theobromine and guanine; caffeïne is present in largest quantity (2–2.5%).

Cocoa-beans (cacao-seed) are characterized by the large content of theobromine (1–4%); they contain, furthermore, a small quantity of caffeïne.

Caffeïne alone is found in the seeds (0.5–2.2%) and in the leaves (1.3%) of the coffee-tree, in Paraguay tea (1.2%), and in guarana (as high as 5%).

Cola-nuts contain caffeïne (2.3%) and a little theobromine (0.02%).

The last four alkaloids of the above series are found in the seeds, buds, and roots of a large number of plants. They also occur quite widely extended in the animal kingdom, having been

observed in almost all the organs of the higher animals. Their occurrence is explained by the fact that they are decomposition-products of *nuclein*, which forms a normal constituent of the cell in both the plant and animal kingdoms.

Through the brilliant investigations of E. Fischer,[1] all these xanthine bases have now been prepared synthetically and they are shown to be derivatives of a nitrogenous ring system, $C_5H_4N_4$, which has received the name *purine.*

Purine, $C_5H_4N_4$.—Purine is the mother-substance not only of the alkaloids mentioned above but also of uric acid, which is formed so universally in the destructive metabolism of animal matter. As we shall now show, this acid is a trioxypurine and from it purine itself may be prepared.

When uric acid is oxidized with nitric acid in the cold, it is decomposed into *mesoxalylurea* (*alloxan*) and *urea:*[2]

$$\underset{\text{Uric acid}}{C_5H_4N_4O_3} + O + H_2O \rightarrow \underset{\text{Alloxan}}{CO\begin{matrix} \diagup NH-CO \diagdown \\ \\ \diagdown NH-CO \diagup \end{matrix}CO} + \underset{\text{Urea}}{CO(NH_2)_2}.$$

This reaction points to the existence in the acid of the two groupings

$$\begin{matrix} N-C \\ | \quad\; | \\ C \quad C \\ | \quad\; | \\ N-C \end{matrix} \quad \text{and} \quad \begin{matrix} N \\ | \\ C \\ | \\ N \end{matrix}$$

Uric acid has been synthesized in various ways,[3] but no synthesis shows more clearly the nature of these groups and their mode of union in the molecule of the acid than does the following of E. Fischer:[4]

---

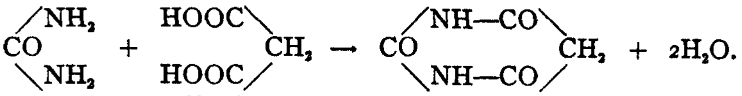
[1] E. Fischer, B. **32**, 435. A review of the author's work on the purine derivatives. *Naturw. Rundschau*, **18**, 157, 169 (1903).

[2] Liebig, Wöhler, A. **26**, 256.

[3] Behrend and Roosen, A. **251**, 235.

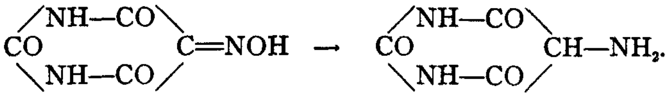
[4] Ach and Fischer, B. **28**, 2473. E. Fischer, B. **30**, 559.

Urea and malonic acid unite under the action of phosphorus oxychloride to form *malonylurea:*



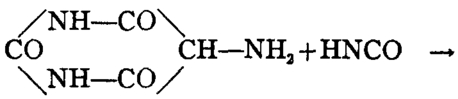
Urea Malonic acid Malonylurea

With nitrous acid this ureïde gives an isonitroso-derivative (*violuric acid*) which on reduction yields amido-malonylurea (*uramil*):

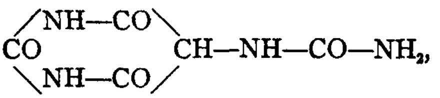


Violuric acid Uramil

Potassium cyanate converts uramil into *pseudo-uric acid,*

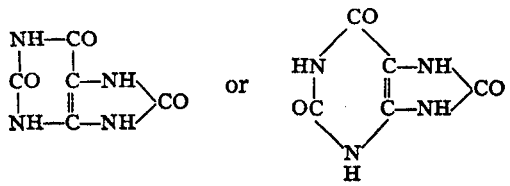


Uramil



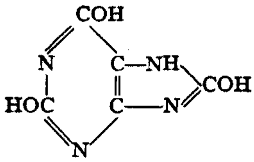
Pseudo-uric acid

and the latter, on being warmed with dilute hydrochloric acid, loses a molecule of water and passes over into *uric acid:*



Uric acid

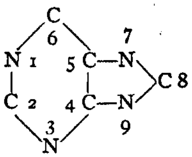
In addition to this "lactame" form of uric acid we may also employ the "lactime" form:



Uric acid

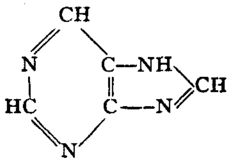
Uric acid derivatives are also known which are derived from the latter formula. In our discussion, however, we shall ordinarily employ the "lactame" form.

For all the derivatives of uric acid the following ring system is characteristic:



In this complex the individual carbon and nitrogen atoms are usually indicated by numbers in the order given.

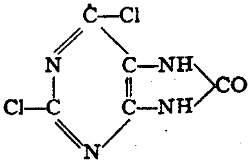
The conversion of uric acid into purine,



Purine

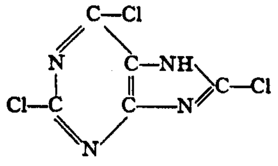
is effected by the following reactions:[5]

When the potassium salt of uric acid is treated with phosphorus oxychloride, there is obtained the derivative $C_5H_2N_4Cl_2$. 8-*oxy*-2,6-*dichlorpurine*,

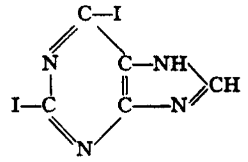


[5] Fischer, B. 17, 1780. Fischer and Ach, B. 30, 2208.

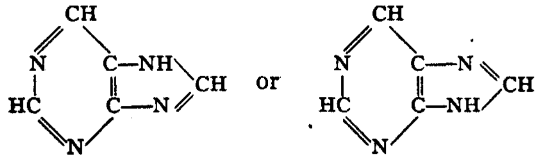
This body, whose constitution was fully established by Fischer, on being heated for four hours at 150° with phosphorus oxychloride, yields *trichlorpurine*,[6]



Hydriodic acid and phosphonium iodide at 0° reduce trichlorpurine to 2,6-*diiodopurine*,



and this latter on reduction with zinc-dust and water forms *purine*,



Purine

Derivatives of both these forms are known.[7]

Purine crystallizes from alcohol in small needles which melt at 216° (corrected). It is readily soluble in water; the solution is without action on litmus.

1. Xanthine.

Xanthine, $C_5H_4N_4O_2$, was discovered by Marcet in 1817 in a urinary calculus. It has been found in the muscles, the liver,

[6] Fischer, B. 30, 2220.
[7] Fischer, B. 32, 448.

and the pancreas of several animals and it has also been noted in guano. It is a normal constituent of urine.

Its occurrence in the vegetable kingdom was shown by Baginsky,[8] who extracted it from tea-leaves; later von Lippmann [9] noted it in the juice of the beet. According to Salomon [10] it is also contained in shoots of the lupine and of barley.

Kossel [11] obtained xanthine by boiling nucleïn with water. It is most advantageously prepared by the action of nitrous acid on guanine.[12]

Xanthine separates from its aqueous solution as a white powder, which is almost insoluble in cold water, very little soluble in hot water, and is insoluble in alcohol and ether. When heated it decomposes without melting with the evolution of carbon dioxide, ammonia, and hydrocyanic acid.

The alkaloid is a weak, monacid base. It possesses also acid properties and unites with bases to form salts which contain two equivalents of metal. These salts are decomposed by carbonic acid.

Electrolytic reduction converts xanthine into *desoxyxanthine*, $C_5H_6ON_4+H_2O$.[13]

Xanthine is the lower homologue of theobromine and caffeïne and by the introduction of methyl groups may be converted into these. Thus theobromine is formed by heating the lead salt of xanthine with methyl iodide to 100°:

$$\underset{\text{Lead salt of xanthine}}{C_5H_2N_4O_2Pb} + 2CH_3I \rightarrow \underset{\text{Theobromine}}{C_5H_2N_4O_2(CH_3)_2} + PbI_2.$$

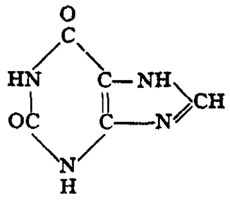
In like manner caffeïne results from heating a solution of xanthine in aqueous alkali with methyl iodide:[14]

$$\underset{\text{Xanthine}}{C_5H_4N_4O_2} + 3CH_3I + 3KOH \rightarrow \underset{\text{Caffeïne}}{C_5HN_4O_2(CH_3)_3} + 3KI + 3H_2O.$$

---

[8] Baginsky, *Zeitschrift für physiologische Chemie*, 8, 395.
[9] Von Lippmann, B. 29, 2645.
[10] Salomon, J. 1881, 1012.
[11] Kossel, *Zeitschrift für physiologische Chemie*, 4, 290.
[12] Fischer, A. 215, 309.
[13] Tafel, B. 33, 2216.
[14] Fischer, B. 31, 2563.

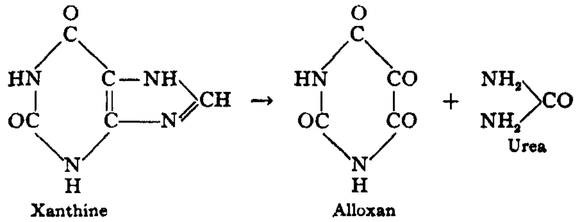
Xanthine is 2,6-*dioxypurine:*



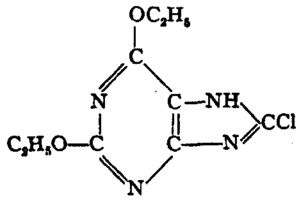
Xanthine

Its structure follows not only from its relation to theobromine and caffeïne, whose constitution is fully developed later (pages 429, 436), but also from the following considerations:

1′. When xanthine is treated with potassium chlorate and hydrochloric acid it is oxidized to alloxan and urea:[15]



2′. When trichlorpurine is heated for three hours at 100° with a concentrated alcoholic solution of sodium ethylate, it is converted into 2,6-*diethoxy-8-chlorpurine* (fine needles, melting-point 205°):



The combined reducing and saponifying action of hydriodic acid at the ordinary temperature changes this to xanthine.[16]

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[15] Fischer, B. 15, 453; A. 215, 311.

[16] Fischer, B. 30, 2232.

3'. If trichlorpurine is reduced to diiodopurine (page 425) and the latter is then heated in a sealed tube for an hour at 100° with a tenfold quantity of concentrated hydrochloric acid, xanthine is formed.[17]

2. CAFFEÏNE.

Caffeïne, or *theïne*, was discovered in 1820 by Runge[18] in coffee, the seed of *Coffea arabica* L. (family of the Rubiaceæ); it is there found in combination with citric and tannic acids. Caffeïne has also been observed in the leaves of the same plant.[19]

It occurs, furthermore, in several other plants; thus it was obtained—

in 1827 by Oudry[20] from tea, the leaves of *Camellia theifera*, or *Thea chinensis* (family of the Ternstrœmiaceæ);

in 1840 by Martins[21] from guarana, a foodstuff which in Brazil is prepared from the seed of *Paullinia sorbilis* Mart. (family of the Sapindaceæ);

in 1843 by Stenhouse[22] from Paraguay tea, the leaves of *Ilex paraguariensis* St. Hilaire (family of the Ilicineæ);

in 1865 by Attfield[23] from the cola-nut, the seed of *Cola acuminata* R. Br. (family of the Sterculiaceæ); and lastly

in 1883 by E. Schmidt[24] from the seed of *Theobroma Cacao* L. (family of the Sterculiaceæ).

The empirical formula of caffeïne is $C_8H_{10}N_4O_2$. It crystallizes from water in lustrous needles which contain one molecule of water; in the anhydrous condition it melts at 234–235°; it sublimes and distils without decomposition. Caffeïne is little soluble in cold water, alcohol, and ether; it dissolves readily, however, in the warm solvent, as also in chloroform and benzol.

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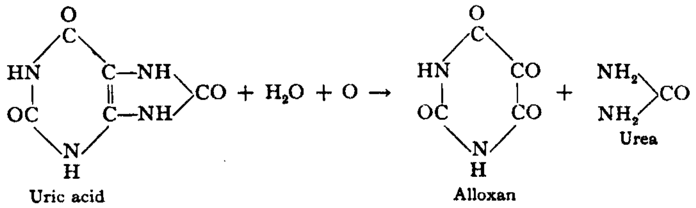
[17] Fischer, B. 31, 2562.
[18] Runge, *Schweigger's Journal für Chemie und Physik*, 31, 308.
[19] Stenhouse, A. 89, 244.
[20] Oudry, *Magazin für Pharmacie*, 19, 49.
[21] Martins, A. 36, 93.
[22] Stenhouse, A. 45, 366; 46, 227.
[23] Attfield, *Pharmaceutical Journal*, [2] 6, 457.
[24] Schmidt, A. 217, 306.

It is a weak base of neutral reaction; its salts are decomposed by water. It behaves ordinarily as a monacid base, but under certain conditions it yields also a dihydrochloride. It possesses a weakly bitter taste and is but slightly poisonous. Both caffeïne and its derivatives are employed as a diuretic.

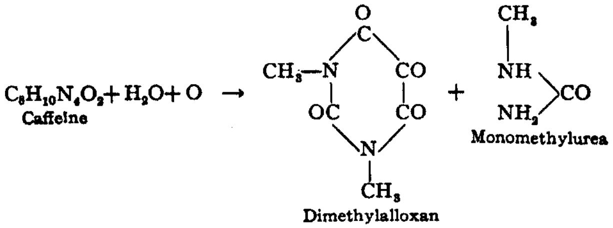
Constitution of Caffeïne.—Caffeïne contains three nitrogen-methyl groups; this follows not only from its formation by the methylation of theobromine and theophylline, in which, as we shall see farther on, two methyl groups are already present, but also from a direct determination of its methyl groups.[25] The formula for caffeïne may accordingly be resolved into $C_5HNO_2(NCH_3)_3$.

The unsaturated nature of the alkaloid is shown in its ability to add bromine; it forms thus an amorphous, unstable dibromide.

The relation of caffeïne to uric acid is indicated first of all by the nature of its oxidation-products. Just as uric acid on treatment with potassium chlorate and hydrochloric acid is decomposed into *alloxan* and *urea*,



so caffeïne under the same treatment is converted into *dimethyl-alloxan* and *monomethylurea*,[26]

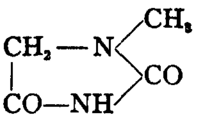


[25] Herzig and Meyer, M. 15, 613.

[26] Rochleder, A. 50, 231; 63, 201; 69, 120; 71, 1. Maly and Andreasch, M. 3, 92.

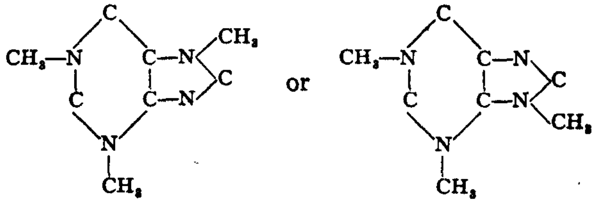
It is not our purpose to speak here of the various relations of caffeïne to uric acid and purine, which have been developed since 1883 in the fruitful investigations of E. Fischer. We shall consequently limit ourselves to the presentation of those points which are necessary to establish the constitution of caffeïne.

Among the decomposition-products of caffeïne, Fischer obtained *methylhydantoïn*,



If this result is compared with that which oxidation gave, we see that the molecule of caffeïne, just as that of uric acid, is formed by the union of two nitrogenous rings, of which one, a hexatomic ring, is found in dimethylalloxan, the other, a pentatomic, in methylhydantoïn. Two methyl groups are, accordingly, contained in the former ring, one in the latter.

The atomic grouping in caffeïne may then be expressed by one of the two following schemes:



Now which of these two represents caffeïne? This question finds answer in the formation of another decomposition-product which Fischer obtained, viz., *dimethyloxamide*,

$$CH_3—NH—CO—CO—NH—CH_3.$$

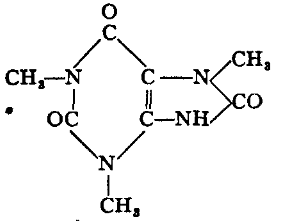
If we consider both the above schemes, we see that only the first possesses an atomic grouping, in which the chain of dimethyl oxamide is contained.

It now remains to determine in this atomic complex the position of the double bond, of the two oxygen atoms, and of the hydrogen atom. This is solved by Fischer from a study of *oxycaffeïne* (*hydroxycaffeïne*).

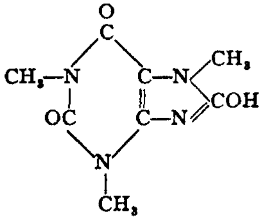
Caffeïne not only adds bromine to form an unstable addition-product, but it also reacts with the halogens to form substitution-products, in which the substituted halogen atom may be readily exchanged for other radicals.

Chlorcaffeïne, $C_8H_9ClN_4O_2$ (needles, melting-point 183°), is thus converted into *methoxycaffeïne*, $C_8H_9N_4O_2(OCH_3)$, on treatment with a solution of caustic soda in methyl alcohol. If now methoxy-caffeïne is boiled with dilute hydrochloric acid, methyl chloride is eliminated and *oxycaffeïne*, ($C_8H_{10}N_4O_3$), is formed.

Oxycaffeïne has been proved by Fischer to be *trimethyluric acid*,

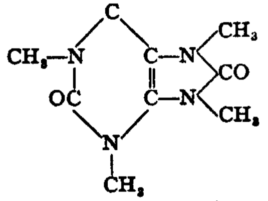


or

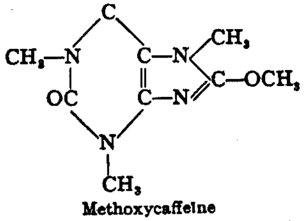


By heating its solution in caustic soda with methyl iodide at 100° we obtain tetramethyluric acid, a substance which is also formed by the direct methylation of uric acid.[27]

If, however, the silver salt of oxycaffeïne is heated with methyl iodide, there results a mixture of tetramethyluric acid and *methoxy-caffeïne:*



Tetramethyluric acid

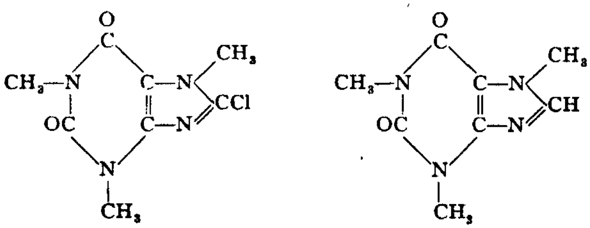


Methoxycaffeïne

[27] Fischer, B. 17, 1776; *Chemiker-Zeitung*, 21, 381.

The simultaneous formation of these two bodies shows that oxycaffeïne may react in two tautomeric forms, characterized by the groupings —NH—CO— and —N═C(OH)—. Now these groups can exist only in the hydantoïn nucleus; in this nucleus, accordingly, must occur the methoxyl of methoxycaffeïne.

Since methoxycaffeïne is derived from chlorcaffeïne, and this in turn from caffeïne by the simple reactions given above, the constitutions of the last two must be expressed as follows:



Chlorcaffeïne Caffeïne

This constitution of caffeïne is fully sustained by the various syntheses of the alkaloid.

Synthesis of Caffeïne.—1′. Strecker[28] obtained the alkaloid in 1861 by heating the silver salt of theobromine with methyl iodide:

$$C_7H_7N_4O_2Ag + CH_3I \rightarrow C_8H_{10}N_4O_2 + AgI.$$

Silver salt of theobromine — Caffeïne

It is also formed by heating free theobromine with an alcoholic solution of methyl iodide.[29]

2′. Kossel[30] prepared caffeïne in 1888 by methylating theophylline (page 437).

3′. In 1898 Fischer[31] obtained caffeïne by the methylation of xanthine:

$$C_5H_4N_4O_2 + 3CH_3I \rightarrow C_8H_{10}N_4O_2 + 3HI.$$

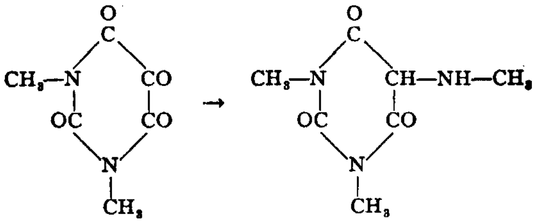
[28] Strecker, A. 118, 151.
[29] Schmidt and Pressler, A. 217, 294.
[30] Kossel, *Zeitschrift für physiologische Chemie*, 13, 305.
[31] Fischer, B. 31, 2563.

The above three syntheses depend on the introduction of alkyls into lower homologues of the alkaloid; those which follow, however, are complete syntheses.

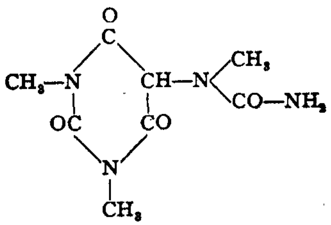
4′. In 1895 Fischer and Ach [32] effected through 1,3-*dimethyl-uric acid* the first complete synthesis of chlortheophylline (page 438). By the introduction of a methyl group the latter was converted into chlorcaffeïne and this in turn on reduction yielded caffeïne.

5′. In 1897 Fischer [33] obtained the alkaloid from dimethyl-alloxan by means of the following reactions:

Dimethylalloxan and neutral methyl ammonium sulphite form an addition-product which concentrated hydrochloric acid converts into *trimethyluramil:*


Dimethylalloxan Trimethyluramil

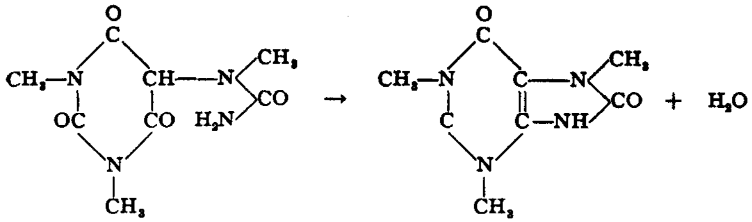
When trimethyluramil is heated with an aqueous solution of potassium cyanate it yields *trimethyl-pseudo-uric acid,*



which on being boiled with dilute hydrochloric acid condenses

[32] Fischer and Ach, B. 28, 3135.
[33] Fischer, B. 30, 559.

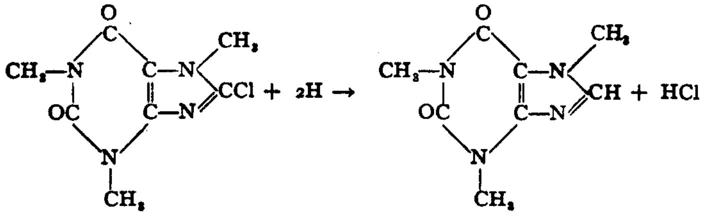
to 1,3,7-*trimethyluric acid*, or *hydroxycaffeïne* (*trimethyltrioxypurine*):



Trimethyl-pseudo-uric acid — Hydroxycaffeïne

Hydroxycaffeïne crystallizes in needles which melt near 345°. It is very little soluble in cold water, alcohol, and ether. It possesses both basic and acid properties.

Phosphorus pentachloride converts hydroxycaffeïne into chlorcaffeïne (1,3,7-*trimethyl-8-chlordioxypurine*), which, on reduction with zinc and hydrochloric acid, yields caffeïne itself:



Chlorcaffeïne — Caffeïne

6'. The same year Fischer[34] succeeded in synthesizing caffeïne directly from uric acid through the intermediate formation of tetramethyluric acid. When the latter is heated with phosphorus oxychloride it is converted into chlorcaffeïne.

7'. In 1898 Fischer[35] synthesized caffeïne from 3-methyluric acid. By the action of phosphorus oxychloride this is changed into 3-methylchlorxanthine:

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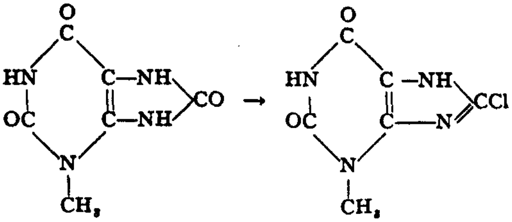
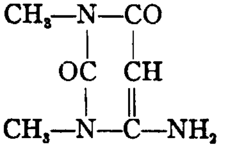
[34] Fischer, B. 30, 3010.
[35] Fischer, B. 31, 1980.



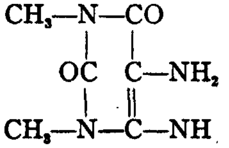
3-Methyluric acid — 3-Methylchlorxanthine

On methylating this last derivative, Fischer obtained *chlor-theobromine*, which he reduced with hydriodic acid to *theobromine*. The conversion of theobromine into caffeïne has already been discussed above.

8′. In 1900 Traube[86] presented a synthesis of the alkaloid from symmetrical dimethylurea, $CH_3NH—CO—NHCH_3$, and cyanacetic acid. By condensation of these two substances he obtained 1,3-*dimethyl*-4-*amido*-2,6-*dioxypyrimidine:*



Reduction of the isonitroso-derivative of this body gave rise to 1,3-*dimethyl*-4,5-*diamido*-2,6-*dioxypyrimidine,*



which boiled with formic acid yields a formyl derivative, $C_7H_{10}O_3N_4$. When this last is heated for several hours with methyl iodide in an alcoholic solution of sodium ethylate, caffeïne is formed.

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[86] Traube, B. 33, 3035.

3. THEOBROMINE.

Theobromine was isolated from cacao-beans by Woskresensky[37] in 1842; it occurs here in combination with malic acid. According to Heckel and Schlagdenhaufen[38] it is also found in small quantity in the cola-nut.

Its formula is $C_7H_8N_4O_2$. It crystallizes in anhydrous, microscopic needles, which at the ordinary temperature are very little soluble in water and alcohol. In ether they are almost entirely insoluble. It sublimes without melting at 290–295°. Heated in a closed tube, however, it melts at 329–330°.[39]

Its physiological properties closely resemble those of caffeïne.

It is a weak, monacid base, neutral in action. Its salts are decomposed by water; it does not combine with alkyl iodides. Unlike caffeïne, this alkaloid possesses acid properties.

Theobromine contains two methyl groups attached to nitrogen.[40] When its potassium or silver salt is heated with methyl iodide, caffeïne is formed;[41] with ethyl iodide *homocaffeïne*, $C_9H_{12}N_4O_2$, results.[42] This last crystallizes in needles which melt at 164–165°.

From this it appears that theobromine is a caffeïne in which one methyl group is replaced by a hydrogen atom.

Which now of the three methyl groups of caffeïne is eliminated in theobromine?

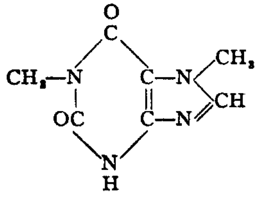
The solution of this question is found in the decomposition of theobromine, which Fischer effected with potassium chlorate and hydrochloric acid; the alkaloid is thus decomposed into *monomethylalloxan* and *monomethylurea*.

We saw that under the same conditions caffeïne yields dimethylalloxan and monomethylurea. From this we conclude that

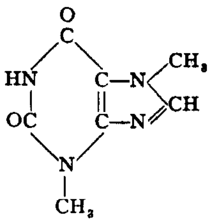
---

[37] Woskresensky, A. 41, 125.
[38] Heckel and Schlagdenhaufen, Bl. [2] 38, 250.
[39] Michael, B. 28, 1629.
[40] Herzig and Meyer, M. 15, 613.
[41] Strecker, A. 118, 151.
[42] Van der Slooten, *Apotheker-Zeitung*, 12, 5.

theobromine has only one methyl group in the alloxan nucleus. The alkaloid consequently is represented by one of the two following formulæ:

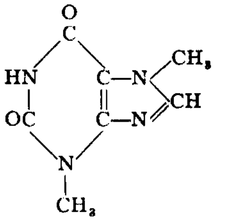


or



Theobromine

Fischer has shown that the second formula is without much doubt the correct one. Theobromine is consequently 3,7-*dimethyl-2,6-dioxypurine* (3,7-*dimethylxanthine*):[43]



A synthesis of theobromine from 3-methyluric acid we have already mentioned (page 434). Since 3-methyluric acid is obtained by directly methylating uric acid, this mode of preparation is quite simple.

Theobromine may be obtained from 3,7-*dimethyluric acid* by heating the latter with phosphorus oxychloride, whereby chlortheobromine is first formed.

It may also be prepared by the action of methyl iodide on the lead salt of xanthine.

4. Theophylline.

This alkaloid, an isomer of theobromine, was isolated from tea-leaves by Kossel[44] in 1888. It crystallizes in plates which

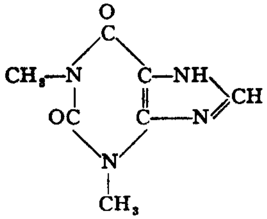
[43] Fischer, B. 15, 32, 453; 32, 435, 469. Maly and Andreasch, M. 1882, 107. Fischer and Ach, B. 31, 1980.

[44] Kossel, B. 21, 2164; *Zeitschrift für physiologische Chemie*, 13, 298.

melt at 264°. It is little soluble in alcohol, but readily soluble in boiling water. Like theobromine, it is a weak, monacid base.

When the silver salt of theophylline is heated with methyl iodide, caffeïne is obtained. Theophylline is, accordingly, like theobromine, a caffeïne, in which a methyl group has been replaced by a hydrogen atom.

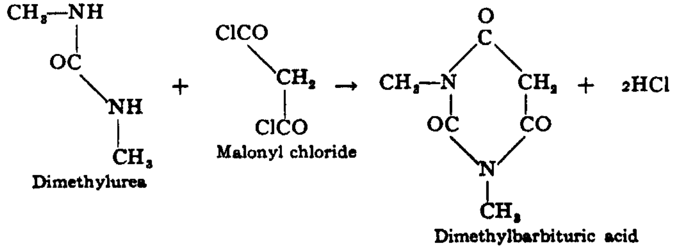
Treated with potassium chlorate and hydrochloric acid, theophylline yields the same *dimethylalloxan* as caffeïne. The two methyl groups of the alloxan nucleus are consequently also present in theophylline, while the hydantoïn nucleus contains no such group. Theophylline is thus 1,3-*dimethyl*-2,6-*dioxypurine*,



Theophylline

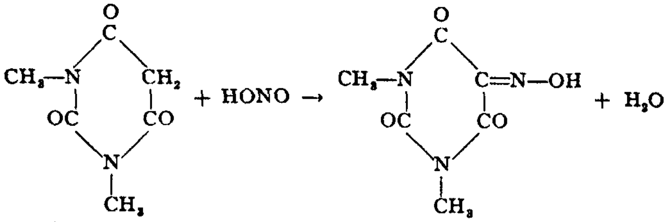
In 1895 Fischer and Ach[45] effected the complete synthesis of theophylline, which as we have already indicated (page 433) also includes that of caffeïne. This was brought about through the following series of reactions:

1'. By successive treatment with phosphorus pentachloride and dimethylurea, malonic acid is converted into *dimethylbarbituric acid:*[46]



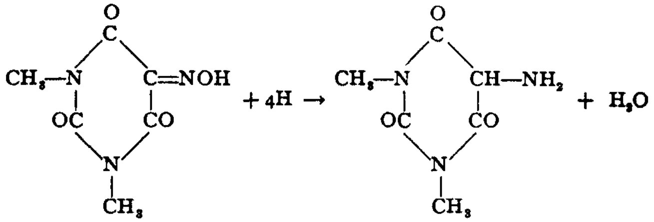
[45] Fischer and Ach, B. 28, 3135.
[46] Mulder, B. 12, 466.

2′. If now to the aqueous solution of dimethylbarbituric acid sodium nitrite is added, we obtain ***dimethylvioluric acid*** (***dimethyl-isonitrosobarbituric acid***):



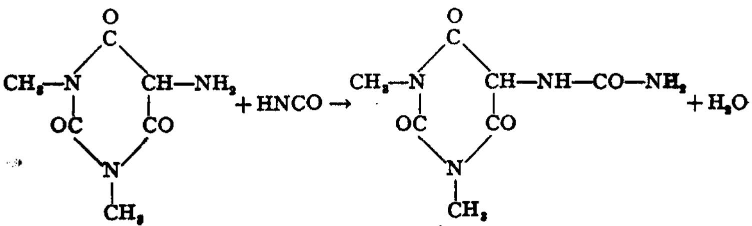
Dimethylbarbituric acid — Dimethylvioluric acid

3′. Reduction of dimethylvioluric acid with hydriodic acid gives rise to ***dimethyluramil:***



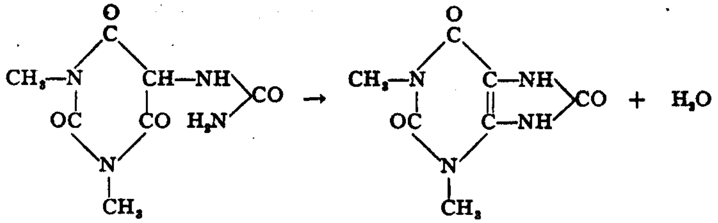
Dimethylvioluric acid — Dimethyluramil

4′. When dimethyluramil is heated at 100° with a concentrated solution of potassium cyanate, ***dimethyl-pseudo-uric acid*** is formed:



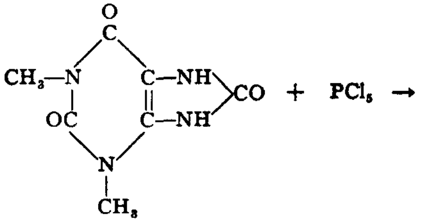
Dimethyluramil — Dimethyl-pseudo-uric acid

5′. Dimethyl-pseudo-uric acid loses a molecule of water when it is heated with oxalic acid or, better still, with hydrochloric acid. The product resulting is 1,3-***dimethyluric acid:***

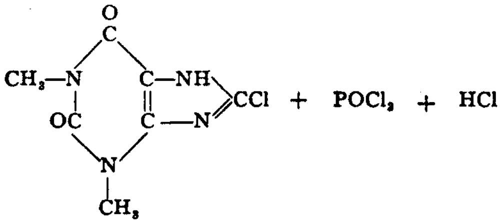


Dimethyl-pseudo-uric acid → Dimethyluric acid

6'. Phosphorus pentachloride and oxychloride convert the latter acid into *chlortheophylline:*



1,3-Dimethyluric acid

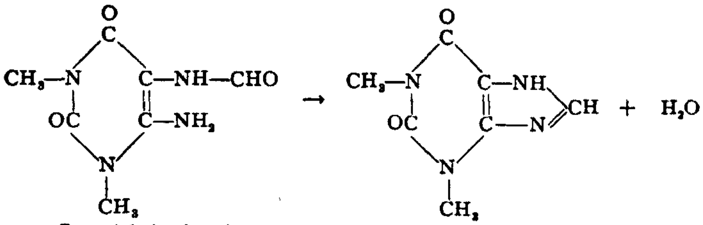


Chlortheophylline

7'. Reduction of chlortheophylline with hydriodic acid at 100° lastly gives rise to *theophylline* itself.

In 1900 Traube[47] synthesized theophylline from symmetrical dimethylurea and cyanacetic acid. The reactions are essentially the same as those employed by him in the synthesis of caffeïne (page 435). When the formyl derivative of 1,3-*dimethyl*-4,5-*diamido*-2,6-*dioxypyrimidine*, which he obtained, is heated to its melting-point (252°), water is eliminated and condensation to theophylline ensues:

47 Traube, B. 33, 3053.



Formyl derivative of 1,3-dimethyl-4,5-diamido-2,6-dioxypyrimidine

Theophylline

A slight modification of this synthesis was recently made the subject of a patent by F. Bayer & Co.[48]

5. Hypoxanthine.

Hypoxanthine, or sarcine, $C_5H_4N_4O$, occurs in both the vegetable and animal kingdoms. It was discovered in milk by Scherer[49] in 1850; since then it has been found in many of the animal liquids and organs (glands, muscles, marrow, blood, urine), and in the seeds of the lupine, barley, mustard, black pepper, the gourd, alfalfa, vetch, clover, and in wheat-bran, potatoes, sugar-beets, and tea.

Hypoxanthine is formed in the plant as in the animal organism by the decomposition of nucleïn. Salomon and Kossel[50] show that nucleïn on putrefaction yields hypoxanthine, as it also does under the action of yeast from beer-fermentation.

The alkaloid crystallizes in microscopic needles which decompose without melting at 150°; it is little soluble in cold water. It exhibits both acid and basic properties and combines with one equivalent of an acid or two equivalents of a base.

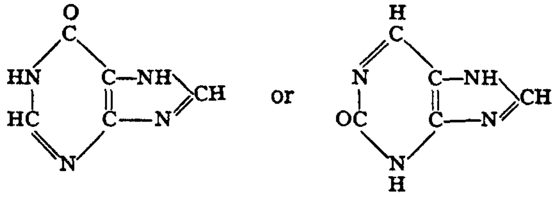
Hypoxanthine closely resembles xanthine. On oxidation with potassium chlorate and hydrochloric acid, it gives the same derivatives as does the latter alkaloid, viz., alloxan and urea. From this reaction we note the close relationship of the two bases

[48] F. Bayer & Co., Patent No. 138444 (1903).

[49] Scherer, A. 73, 328.

[50] Salomon, *Zeitschrift für physiologische Chemie*, 2, 190. Kossel, *ibid.*, 5, 152, 167.

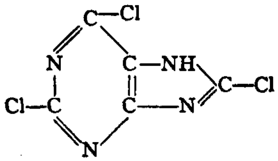
to each other. Since hypoxanthine differs from xanthine only in possessing one less oxygen atom, we must assign to the former alkaloid one of the two following formulæ:



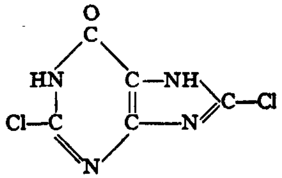
Hypoxanthine

The further investigations of hypoxanthine by Fischer[61] led to his acceptance of the first of these formulæ—a conclusion which is supported by the following two syntheses:

1′. When trichlorpurine (page 425),



is heated for some time with an alkali, the chlorine atom in position 6 is eliminated and there is obtained *6-oxy-2,8-dichlorpurine* (dichlorhypoxanthine),



Reduction with hydriodic acid converts this derivative into hypoxanthine.

2′. Under the action of nitrous acid, *adenine*, whose constitution is regarded as

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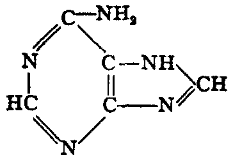
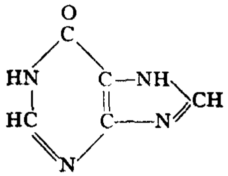
[61] Fischer, B. 30, 2228.



is changed to hypoxanthine.

Hypoxanthine is, accordingly, 6-*oxypurine:*



Hypoxanthine

6. Guanine.

Guanine was discovered in guano by Unger[52] in 1844. Since then it has been found in the tissues and excrements of different animals. It appears also to be somewhat widely diffused throughout the vegetable kingdom; Schulze[53] found it in the seeds of several leguminous plants (the vetch, alfalfa, clover) and in those of the gourd; Ullik[54] obtained it from germinated barley, von Lippmann[55] from the sugar-beet, and Shorey[56] from cane-sugar.

Guanine, C_5H_5NO, crystallizes from ammonia in needles or small plates which are insoluble in water, alcohol, and ether. It is neutral in reaction and dissolves in both acids and alkalies to form salts in which it functionates on the one hand as a diacid base, and on the other as a dibasic acid.

Guanine is 2-*amido*-6-*oxypurine:*

---

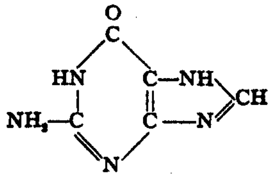
[52] Unger, A. 51, 395; 58, 18; 59, 58.

[53] Schulze, *Zeitschrift für physiologische Chemie*, 9, 420; 10, 80, 326; J. pr. [2] 32, 433.

[54] Ullik, *Chemisches Centralblatt*, 1887, 829.

[55] Lippmann, B. 29, 2645.

[56] Shorey, *Jour. Am. Chem. Soc.* 27, 609.

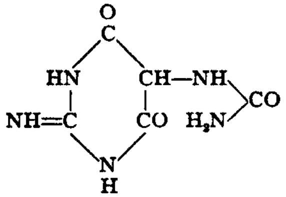


Guanine

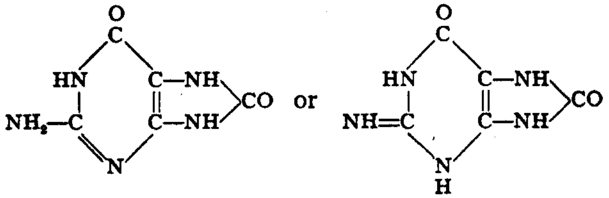
Its constitution is shown by the following considerations:

Guanine is closely related to xanthine (2,6-dioxypurine), since nitrous acid converts it into the latter (page 425).[57]

When guanine is heated with bromine to 150°, there is obtained a substitution-product of the formula $C_5H_4BrN_5O$.[58] If this bromguanine is treated with concentrated hydrochloric acid at 130°, it passes over into *oxyguanine*, $C_5H_5N_5O_2$ (a crystalline powder). This oxyguanine was also prepared by Fischer[59] by the action of hydrochloric acid at 130° on the *imido-pseudo-uric acid* of Traube,[60] the constitution of which is definitely established by its synthesis from guanidine and malonic ester (analogous to the synthesis of uric acid):



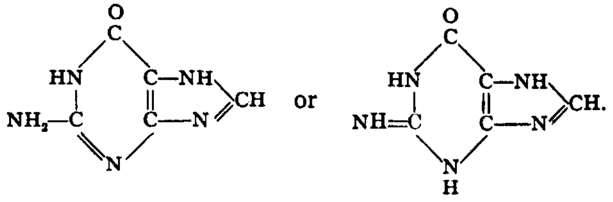
Imido-pseudo-uric acid



Oxyguanine

[57] Strecker, A. 108, 141; 118, 151. Fischer, A. 215, 309.
[58] Fischer and Reese, A. 221, 342.
[59] Fischer, B. 30, 559.
[60] Traube, B. 26, 2551.

From these formulæ for oxyguanine we derive the following tautomeric forms for guanine:

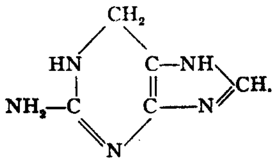


Guanine

In his later investigations Fischer[61] succeeded in synthesizing guanine from *6-oxy-2,8-dichlorpurine* (*dichlorhypoxanthine*, page 442). Alcoholic ammonia converts this into chlorguanine and the latter on reduction with hydriodic acid yields guanine.

Traube[62] has synthesized guanine from cyanacetic acid and guanidine through the intermediate formation of 2,4-*diamido-6-oxypyrimidine.*

On electrolytic reduction guanine yields an unstable base, *desoxyguanine* (*2-amido-1,6-dihydropurine*):[63]



Desoxyguanine

7. ADENINE.

Adenine, $C_5H_5N_5$, was isolated in 1885 by Kossel[64] from the pancreas of the ox. It is found also in tea, in the juice of the sugar-beet, and is formed in the decomposition of nucleïn by dilute sulphuric acid. It crystallizes from water or ammonia

[61] Fischer, B. 30, 2251.

[62] Traube, B. 33, 1371.

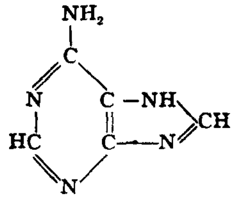
[63] Tafel and Ach, B. 34, 1170.

[64] Kossel, *Zeitschrift für physiologische Chemie*, 10, 250; 12, 241; B 18, 79; 19, 28; 20, 3356.

in long needles which contain three molecules of water. When rapidly heated the anhydrous alkaloid melts with decomposition at 360–365°. It dissolves readily in hot water, is little soluble in cold water and alcohol, insoluble in ether and chloroform. It is neutral in reaction, and forms salts with one equivalent of an acid or a base.

With bromine adenine yields a monobrom-derivative which oxidation with potassium chlorate and hydrochloric acid converts into alloxan, urea, and oxalic acid.

Nitrous acid changes adenine to hypoxanthine. There accordingly subsists between these two derivatives the same relation as between guanine and xanthine. Adenine is consequently 6-*amidopurine:*



Adenine

Adenine is most simply synthesized by the reduction of 6-*amido*-2,8-*dichlorpurine* with hydriodic acid. This dichlor-derivative is obtained by the action of ammonia on trichlorpurine.[65]

To these bases of the xanthine series must be added two other alkaloids which have as yet been little studied:

Carnine, $C_7H_8N_4O_3$.—This substance was discovered in 1871 by Weidel[66] in extract of beef. It is also found in yeast from beer fermentation,[67] and in sugar-beets.[68] It crystallizes from hot water with one molecule of the solvent; on being heated it decomposes at 239°; it is neutral in reaction and possesses both basic and acid properties. Heated with hydrochloric, hydrobromic, or nitric acid, it is converted into *hypoxanthine.*

[65] Fischer, B. 30, 2238.
[66] Weidel, A. 158, 353.
[67] Schützenberger, Bl. [2] 21, 204.
[68] von Lippmann, B. 29, 2645.

Vernine, $C_{16}H_{20}N_8O_8$.—This is found in the young shoots of the vetch, of clover, and of the gourd; in the pollen of the hazel and of the pine;[69] further, in germinated barley[70] and in the sugar-beet.[68]

It forms microscopic prisms containing three molecules of water of crystallization. It is soluble in alkalies and dilute acids; it reacts as a dibasic acid. Boiling hydrochloric acid decomposes vernine into *guanine*.

[69] Schulze, *Zeitschrift für physiologische Chemie*, 9, 420; 10, 80, 226; J. pr. [2] 32, 433.

[70] Ullik, *Chemisches Centralblatt*, 1887, 829.

CHAPTER XXXIV.

ALLANTOÏN.

ALLANTOÏN was discovered in 1800 by Vauquelin and Buniva [1] in the amniotic fluid of the cow, and was later also obtained from the urine of different animals. Allantoïn likewise occurs in the vegetable kingdom. Schulze and Barbieri [2] isolated it from the buds of the plane-tree (*Platanus orientalis* L., family of the Platanaceæ) (0.5–1%). It is also found in the buds of the maple, in the bark of the horse-chestnut tree,[3] in wheat,[4] and in the molasses of the sugar-beet.[5]

Its formula is $C_4H_6N_4O_3$. It crystallizes in prisms which are little soluble in cold water, but somewhat soluble in hot; in alcohol they are almost insoluble. It is neutral in reaction and exhibits the properties of a monacid base and of a monobasic acid.

The constitution of allantoïn to a certain extent approaches the structural complex of the xanthine bases. It is expressed by one of the two following formulæ:

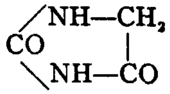
```
  /NH—CH—NH—CO—NH2          /NH—C=N—CO—NH2
CO     |              or  CO     |
  \NH—CO                    \NH—CHOH
```

This constitution follows both from the decomposition and from the synthesis of the alkaloid. Treated with water at 110–

[1] Vauquelin and Buniva, *Annales de chimie*, 33, 269.
[2] Schulze and Barbieri, B. 14, 1602, 1834.
[3] Schulze and Bosshard, *Zeitschrift für physiologische Chemie*, 9, 425.
[4] Richardson and Crampton, B. 19, 1130.
[5] von Lippmann, B. 29, 2645.

140°, with alkalies, with lead peroxide, or with nitric acid, allantoïn yields urea and *allanturic acid* (*glyoxyl urea*).

Hydriodic acid reduces it to urea and *hydantoïn* (*glycolyl urea*):



Hydantoïn

The synthesis of allantoïn was effected by Grimaux[6] in 1877 by heating urea with glyoxylic acid to 100°:

$$2CH_4N_2O + C_2H_4O_4 \rightarrow C_4H_6N_4O_3 + 3H_2O.$$

Michael[7] also obtained it from the action of mesoxalic acid on urea:

$$2CH_4N_2O + C_3H_4O_6 \rightarrow C_4H_6N_4O_3 + 3H_2O + CO_2.$$

Allantoïn is formed in the oxidation of uric acid with lead peroxide or manganese dioxide.[8]

[6] Grimaux, A. ch. [5] 11, 389.
[7] Michael, Am. Chem. Jour. 5, 198.
[8] Claus, B. 7, 226. Fischer and Ach, B. 32, 2721.

CHAPTER XXXV.

THE ASPARAGINE GROUP.

In the vegetable kingdom there is found a group of weakly basic substances which may be designated from its representative member, *asparagine*, as the asparagine group.

This group comprises the following:

1. Aspartic acid....................	$C_4H_7NO_4$.
2. Asparagine (dextro- and lævo-)....	$C_4H_8N_2O_3$.
3. Glutaminic acid..................	$C_5H_9NO_4$.
4. Glutamine.......................	$C_5H_{10}N_2O_3$.
5. Alanine.........................	$C_3H_7NO_2$ and its derivatives.
a. Phenylalanine................	$C_9H_{11}NO_2$.
b. Tyrosine....................	$C_9H_{11}NO_3$.
c. Surinamine..................	$C_{10}H_{13}NO_3$.
6. Leucine.........................	$C_6H_{13}NO_2$.
7. Arginine........................	$C_6H_{14}N_4O_2$.
8. Lysine..........................	$C_6H_{14}N_2O_2$.
9. Histidine.......................	$C_6H_9N_3O_2$.

These substances form not final but intermediate products in the vital processes of the plant; they appear chiefly at the time of germination and often increase to very considerable quantities (particularly is this the case when the growth occurs in the dark); in the sprouts of the lupine asparagine has been found to the extent of 30%. During the growth of the plant they gradually decrease in quantity and disappear almost entirely at the time of the flowering of the plant. This transitional existence distinguishes these bases from all the other alkaloids hitherto considered.

Asparagine and the bases most closely related to it serve the plant through their high nitrogen content above all as foodstuffs for further growth, particularly for the building up of

protoplasm. They are consequently found widely distributed throughout the entire vegetable kingdom, while in the case of the alkaloids already discussed we have noted that an alkaloid and its homologues are usually confined to a few plant species.

In particularly large quantities do we meet these asparagine derivatives in the extensive families of the Leguminosæ and the Cruciferæ. They are found there not only in the young sprouts, but also in the roots, root-bulbs, stems, buds, in short, in all the parts in which reserve material is stored up to serve for the further nourishing of the plant during the period of growth.

Doubtless these substances are formed, for the most part at least, by the decomposition of proteïn substances (legumin, conglutin, globulin, etc.), which accumulate in such large quantities, particularly in the seed. They have, indeed, been obtained by the direct decomposition of albumins of different origin, either by their putrefaction or by purely chemical means as the action of mineral acids, of alkalies, or of barium hydroxide. Animal albumins yield under these conditions the same products as vegetable. We are consequently led to conclude that the existence of leucine and tyrosine in the animal organism is due to the same cause as that which gives rise to these substances in the plant.

Once formed in the young plant by the decomposition of the reserve store of albuminous matter, the asparagine derivatives last only for a short time. As soon as the formation of chlorophyl and the assimilation of carbon dioxide lead to the production of carbohydrates, the asparagine derivatives take part in the vital processes and are changed into albumins and living protoplasm.

In their chemical properties the members of the asparagine group are well defined.

They are primary bases; their nitrogen, consequently, does not form part of a ring. Furthermore, they possess one or two carboxyl groups. By the action of nitrous acid they lose the amide group and are converted into oxy-acids with the group $-CH\langle^{OH}_{COOH}$; they accordingly all contain the common group

$—CH\langle^{NH_2}_{COOH}$. The most of these derivatives are members of the fatty series, though some (phenylalanine, tyrosine, surinamine) contain an aromatic nucleus.

1. ASPARTIC ACID.

Aspartic acid, $C_4H_7NO_4$, is found in young sugar-cane and in the molasses of the sugar-beet.[1] It has also been observed in diseased liver.[2] It is formed by boiling *l*-asparagine with alkalies or with mineral acids.[3] It is obtained also in the hydrolysis of caseïn, glue, etc.[4]

Aspartic acid crystallizes in prisms which are little soluble in alcohol and cold water, but are somewhat more readily soluble in hot water. The acid is dextrorotatory in aqueous solution. If the solution is heated, its rotatory power gradually decreases; at 75° it is inactive and at a still higher temperature it becomes lævorotatory.[5] The natural aspartic acid is dextrorotatory in acid, lævorotatory in alkaline solution. On being heated with water or ammonia at 150°, or with hydrochloric acid at 170–180°, it yields the racemic form, *inactive aspartic* acid.[6] This last is also obtained by mixing natural aspartic acid with the acid which results from the decomposition of *d*-asparagine (page 454).[7]

The aspartic acids form the three stereoisomeric modifications of amido-succinic acid:

$$COOH—CH_2—CH\langle^{NH_2}_{COOH}$$

This follows:

1′. From the conversion of the aspartic acids through the action of nitrous acid into the corresponding malic acids:[8]

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[1] Scheibler, J. 1866, 399.
[2] Taylor, *Zeitschrift für physiologische Chemie*, **34**, 580.
[3] Plisson, A. ch. [2] **35**, 175; **37**, 81; **40**, 303; **45**, 304.
[4] Fischer, *Zeitschrift für physiologische Chemie*, **33**, 151; **35**, 70; **36**, 462.
[5] Cook, B. **30**, 294.
[6] Michael and Wing, B. **17**, 2984.
[7] Piutti, C. r. **103**, 135; B. **19**, 1694.
[8] Piria, A. ch. [3] **22**, 160.

$$\underset{\text{Aspartic acids}}{\begin{array}{l}CH(NH_2)\text{—}COOH\\ |\\ CH_2\text{—}COOH\end{array}} + HONO \rightarrow \underset{\text{Malic acids}}{\begin{array}{l}CH(OH)\text{—}COOH\\ |\\ CH_2\text{—}COOH\end{array}} + N_2 + H_2O.$$

The natural aspartic acid forms *l*-malic acid; the inactive aspartic acid, the inactive malic acid.

2′. From several syntheses of inactive aspartic acid, particularly from that which Piutti[9] effected by reducing the ester of oximido-succinic acid with sodium amalgam:

$$\underset{\text{Oximido-succinic ester}}{\begin{array}{l}C(NOH)\text{—}COOC_2H_5\\ |\\ CH_2\text{—}COOC_2H_5\end{array}} + 4H + 2NaOH \rightarrow$$

$$\underset{\text{Sodium aspartate}}{\begin{array}{l}CH(NH_2)\text{—}COONa\\ |\\ CH_2\text{—}COONa\end{array}} + 2C_2H_5OH + H_2O.$$

Inactive aspartic acid has been separated by Fischer[10] into its optically active forms.

2. ASPARAGINE.

Asparagine has been found in a large number of plants. It occurs in these in two optically active forms which differ from each other only in the sign of their rotatory power.

Lævo-asparagine was discovered in 1805 by Vauquelin and Robiquet[11] in the young shoots of asparagus (*Asparagus officinalis* L., family of the Liliaceæ). It is only slightly soluble in cold water; in hot water it dissolves readily and separates from the cooled solution in large prisms, which contain a molecule of water and which after dehydration melt at 234–235°.[12]

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[9] Piutti, *Atti della reale Academia dei Lincei*, 1887, [2] 300.

[10] Fischer, B. **32**, 2451.

[11] Vauquelin and Robiquet, *Annales de Chimie*, **57**, 88.

[12] Michael, B. **28**, 1629.

It is almost insoluble in alcohol and ether; it reacts weakly acid and possesses an insipid, somewhat disagreeable taste. As we have noted above, it is lævorotatory and retains the direction of its rotation also in alkaline solution; in acid solution, however, it is dextrorotatory.

Dextro-asparagine was discovered in 1886 by Piutti[13] in young shoots of vetches (*Vicia sativa* L., family of the Leguminosæ). It resembles its isomer in every respect save that, strangely enough, it is sweet and agreeable to the taste. This asparagine is dextrorotatory in neutral or alkaline solution, lævorotatory in acid.

It has not been found possible to produce the inactive asparagine by a union of the two active modifications. Such a combination has also not been observed in the plant. An inactive asparagine (α-asparagine) is, however, known. This has been prepared synthetically from inactive aspartic acid (see the following pages).

The asparagines are the monamides of the aspartic acids. Heated with water in a sealed tube, they are converted into ammonium aspartates.[14]

By the action of acids and of alkalies the asparagines are decomposed into aspartic acids and ammonia.[15] Each of the three asparagine modifications yields then the corresponding aspartic acid

$$\underset{\text{Asparagine}}{(C_2H_5N)\langle{}^{COOH}_{CO-NH_2}} + H_2O \rightarrow \underset{\text{Ammonium aspartate}}{(C_2H_5N)\langle{}^{COOH}_{COONH_4}} \rightarrow$$

$$\underset{\text{Aspartic acid}}{(C_2H_5N)\langle{}^{COOH}_{COOH}} + NH_3$$

By reversing this reaction Piutti[16] succeeded in synthesizing

[13] Piutti, C. r. 103, 135.
[14] Boutron and Pelouze, A. ch. 52, 90.
[15] Plisson, A. ch. [2] 35, 175; 37, 81; 40, 303; 45, 304.
[16] Piutti, G. 17, 126; 18, 457.

the asparagines from inactive aspartic acid. When this was converted into its monoethyl ester and the latter was heated with alcoholic ammonia, he obtained together with inactive asparagine a mixture of the two active asparagines, which he was able to separate mechanically by picking out the hemihedral crystals of opposite form:

$$\underset{\text{Monoethyl aspartate}}{(C_2H_5N)\left\langle\begin{array}{l}COOH\\COOC_2H_5\end{array}\right.} + NH_3 \rightarrow \underset{\text{Asparagine}}{(C_2H_5N)\left\langle\begin{array}{l}COOH\\CO{-}NH_2\end{array}\right.} + C_2H_5OH.$$

The proof that the asparagines are the monamides of the aspartic acids is, however, not alone sufficient completely to establish their constitution. As we may readily see, the aspartic acids are able to yield two isomeric monamides, corresponding to the two formulæ,

$$\begin{array}{l}NH_2{-}CH{-}COOH\\ \qquad\ |\\ \qquad CH_2{-}CO{-}NH_2\\ \qquad\quad \text{I}\end{array} \quad \text{and} \quad \begin{array}{l}NH_2{-}CH{-}CO{-}NH_2\\ \qquad\ |\\ \qquad CH_2{-}COOH\\ \qquad\quad \text{II}\end{array}$$

Which of these formulæ, now, represents the asparagines?

This question has been answered by the investigations of Piutti.[17] By the reduction of oximido-oxalic ester,

$$\begin{array}{l}HON{=}C{-}COOC_2H_5\\ \qquad\quad |\\ \qquad\quad CH_2{-}COOC_2H_5\end{array}$$

with sodium amalgam and the partial saponification of the product thus resulting, he obtained two different monoethyl esters of aspartic acid; one melts at 165°, the other at 200°.

Indeed, two such derivatives are to be expected, depending on which of the two ethyl groups is eliminated in the saponification:

[17] Piutti, G. 18, 457.

$$\begin{array}{ccc} NH_2\text{—}CH\text{—}COOH & & NH_2\text{—}CH\text{—}COOC_2H_5 \\ | & \text{and} & | \\ CH_2\text{—}COOC_2H_5 & & CH_2\text{—}COOH \\ \text{III} & & \text{IV} \end{array}$$

Ebert[18] had already obtained by the decomposition of succinylo-succinic ester a monoethyl ester of oximido-succinic acid, to which must be assigned the formula

$$\begin{array}{l} HON{=}C\text{—}COOC_2H_5 \\ \quad\quad\;\; | \\ \quad\quad CH_2\text{—}COOH \end{array}$$

since by the elimination of carbon dioxide it is converted into oximido-propionic ester:

$$\begin{array}{l} HON{=}C\text{—}COOC_2H_5 \\ \quad\quad\;\; | \\ \quad\quad CH_3 \end{array}$$

Now Piutti found that when the above oximido-succinic ester was reduced with sodium amalgam, it yielded that monoethyl ester of aspartic acid which melts at 165°. The latter is accordingly represented by formula IV, while its isomer which melts at 200° must be expressed by formula III.

On treating these two aspartic esters with alcoholic ammonia Piutti succeeded in replacing the ethyl group in each with the amide group. He thus obtained two monamides represented by formulas I and II.

The ester melting at 165° (formula IV) thus gave rise to an inactive asparagine, α-asparagine (formula II).

The ester melting at 200° (formula III) yielded, on the other hand, a mixture of *d*- and *l*-asparagine. The constitution of the latter is consequently expressed by formula I.

It thus appears that inactive or α-asparagine is not structurally identical with the β-asparagines.

The asparagines are without particular physiological action.

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[18] Ebert, A. 229, 45.

Recent investigation [19] points to their occurrence in the plant as *secondary* decomposition-products of albuminous substances, the primary products being amido-acids and hexone-bases.

3. Glutaminic Acid.

Glutaminic acid, $C_5H_9NO_4$, was first obtained by Ritthausen [20] in 1866 by boiling albuminoid substances with dilute sulphuric acid. It occurs in the molasses from beet-root [21] and in the sprouts of vetches and gourds.[22]

It forms crystals which are little soluble in cold water, insoluble in alcohol and in ether; it melts with decomposition at 208°. In neutral and acid solution, this, the ordinary glutaminic acid, is dextrorotatory; in alkaline, lævorotatory. When it is heated with baryta-water to 150° it is converted into *inactive glutaminic acid,* which melts at 198°. By repeated crystallization from water this inactive acid may be separated into its two active constituents.[23] This separation may also be effected through the strychnine salt of benzoylglutaminic acid.[24] Lævo-glutaminic acid may further be obtained from the inactive form by means of *Penicillium glaucum.* The lævorotatory acid presents the same appearance and behavior as the ordinary variety. In acid solution, however, it turns the plane of polarized light to the left.[25]

When glutaminic acid is treated with nitrous acid, there is obtained a hydroxy-acid, $C_5H_8O_5$ (γ-hydroxyglutaric acid), which on reduction with hydriodic acid passes over into glutaric acid:[26]

$$COOH—CH_2—CH_2—CH_2—COOH.$$

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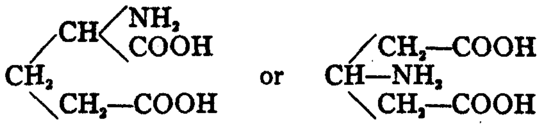
[19] Balicka-Iwanowska, *Anz. Akad. Wiss. Krakau,* 1903, 9.
[20] Ritthausen, J. pr. 99, 6, 454.
[21] Scheibler, B. 2, 296.
[22] Gorup-Besanez, B. 10, 780.
[23] Menozzi and Appioni, *Atti della reale Academia dei Lincei,* 1891, [1] 33.
[24] Fischer, B. 32, 2451.
[25] Schulze and Bosshard, *Zeitschrift für physiologische Chemie,* 10, 143.
[26] Ritthausen, J. pr. 103, 239.

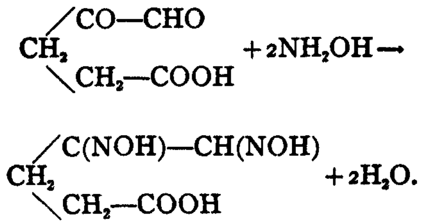
From this glutaminic acid appears to be an amido-derivative of glutaric acid:



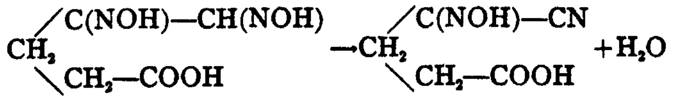
Now since glutaminic acid is optically active it must contain in its molecule an asymmetric carbon atom and must accordingly possess the constitution represented by the former of the formulæ in question.

This formula for the acid is confirmed by the synthesis of inactive glutaminic acid, which was effected by Wolff [27] by means of the following reactions:

1′. Glyoxylpropionic acid with hydroxylamine yields a dioxime (diisonitrosovaleric acid):

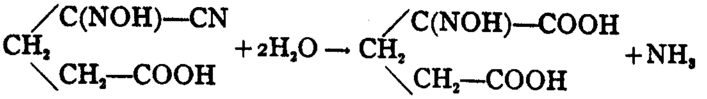


2′. On successive treatment with concentrated sulphuric acid and cold sodium hydroxide this dioxime is converted into isonitrosocyanbutyric acid:

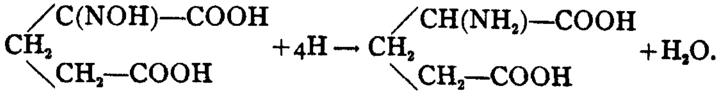


3′. When the latter is saponified with alkalies it gives rise to isonitrosoglutaric acid:

[27] Wolff, A. 260, 79.



4′. On reduction of the last derivative with zinc and hydrochloric acid inactive glutaminic acid is formed:

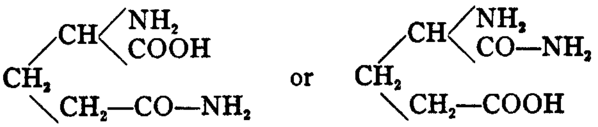


4. Glutamine.

Glutamine, $C_5H_{10}N_2O_3$, is also somewhat widely diffused throughout the vegetable kingdom. It seems to take the place of its lower homologue, asparagine, in certain families, particularly in that of the Cruciferæ. It was discovered in 1877 by Schulze and Urich [28] in beet-roots.

It crystallizes in fine needles which are somewhat readily soluble in water, insoluble in alcohol. In neutral solution it is inactive; in acid, dextrorotatory.

When glutamine is boiled with baryta-water it is decomposed into glutaminic acid and ammonia; it accordingly appears to be the monamide of this acid:



I — II

The experimental data leading to a choice between these two formulæ are as yet lacking. From analogy with asparagine and the other bases of the same group, which all have the free carboxyl and the amide group attached to the same carbon atom, formula I appears to be much the more probable.

[28] Schulze and Urich, B. 10, 85. Schulze and Bosshard, B. 16, 312. E. Schulze, B. 29, 1882.

5. ALANINE.

Alanine, $C_3H_7NO_2$, has been obtained by the decomposition of the legumin contained in peas.[29] The composition is brought about by heating the proteïd with barium hydroxide.

Alanine is of particular interest, since it forms the mother-substance of *phenylalanine* and *tyrosine*, bases which are found in many plants.

Alanine (inactive) crystallizes in needles which melt with decomposition at 293°. It dissolves readily in water, more difficultly in alcohol, and is insoluble in ether.

From the inactive form may be derived the active alanines (melting-point 297°). These show only a weak rotatory power, which in acid solution, however, is considerably increased.[30]

Alanine is *α-amidopropionic acid:*

$$CH_3-CH\langle^{NH_2}_{COOH}$$

Its constitution is shown not only from its conversion into α-lactic acid by means of nitrous acid, but also from the following two syntheses:

1′. From α-chlorpropionic by treatment with ammonia:[31]

$$CH_3-CH\langle^{Cl}_{COOH} + NH_3 \rightarrow CH_3-CH\langle^{NH_2}_{COOH} + HCl$$

2′. From aldehyde-ammonia and prussic acid under the action of hydrochloric acid:[32]

$$CH_3-CH\langle^{NH_2}_{OH} + HCN \rightarrow \underset{\alpha\text{-Amidopropionitrile}}{CH_3-CH\langle^{NH_2}_{CN}} + H_2O.$$

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[29] Blennard, A. ch. [5] 26, 47.
[30] Fischer, B. 32, 2451.
[31] Kolbe, A. 113, 220.
[32] Strecker, A. 75, 29.

$$CH_3-CH\begin{matrix}/NH_2\\ \backslash CN\end{matrix} + 2H_2O \rightarrow \underset{\text{Alanine}}{CH_3-CH\begin{matrix}/NH_2\\ \backslash COOH\end{matrix}} + NH_3$$

This constitution is further confirmed by the transformation of *d*-alanine into *d*-lactic acid, when a solution of the former in hydrochloric acid is treated with silver nitrite.[33]

a. **Phenylalanine,** $C_9H_{11}NO_2$, was isolated by Schulze and Barbieri[34] from lupine sprouts. It crystallizes in prisms or in leaflets which are little soluble in cold water and alcohol, insoluble in ether. It melts with decomposition at 263–265°.

Phenylalanine is *β-phenyl-α-amidopropionic acid:*

$$C_6H_5-CH_2-CH\begin{matrix}/NH_2\\ \backslash COOH\end{matrix}$$

This constitution is proved by both the following syntheses:[35]

1′. Phenylacetaldehyde and hydrocyanic acid unite to form the nitrile of *β*-phenyllactic acid:

$$C_6H_5-CH_2-CHO + HCN \rightarrow C_6H_5-CH_2-CH\begin{matrix}/OH\\ \backslash CN\end{matrix}$$

From the action of ammonia on this, there is obtained the nitrile of *β-phenyl-α-amidopropionic acid:*

$$C_6H_5-CH_2-CH\begin{matrix}/NH_2\\ \backslash CN\end{matrix}$$

On saponification with hydrochloric acid the last derivative is converted into phenylalanine:

$$C_6H_5-CH_2-CH\begin{matrix}/NH_2\\ \backslash COOH\end{matrix}$$

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[33] Fischer and Skita, *Zeitschrift für physiologische Chemie*, 33, 177.

[34] Schulze and Barbieri, B. 12, 1924; 14, 1785; 16, 1711.

[35] Erlenmeyer and Lipp, A. 219, 170. Erlenmeyer, jun., A. 275, 13.

2'. Under the influence of sodium and sodium alcoholate, benzaldehyde and hippuric acid condense to benzoylamido-cinnamic ester:

$$C_6H_5{-}CH\begin{cases} ONa \\ OC_2H_5 \end{cases} + H_2C\begin{cases} NH{-}COC_6H_5 \\ COOC_2H_5 \end{cases} \rightarrow$$

$$C_6H_5{-}CH{=}C\begin{cases} NH{-}COC_6H_5 \\ COOC_2H_5 \end{cases} + C_2H_5OH + NaOH.$$

When this condensation-product is reduced with sodium-amalgam, we obtain α-benzoylamidophenylpropionic acid. If the latter is now heated with concentrated hydrochloric acid to 150°, decomposition takes place into alcohol, benzoic acid, and phenylalanine:

$$C_6H_5{-}CH_2{-}CH\begin{cases} NH{-}COC_6H_5 \\ COOC_2H_5 \end{cases} + 2H_2O \rightarrow$$

$$\underset{\text{Phenylalanine}}{C_6H_5{-}CH_2{-}CH\begin{cases} NH_2 \\ COOH \end{cases}} + C_6H_5COOH + C_2H_5OH.$$

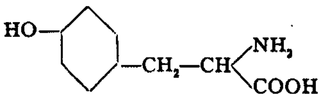
Inactive phenylalanine may be separated into the *d*- and *l*-modifications through the cinchonine salt of the benzoyl derivative.[36] *d*-Phenylalanine is the optical isomer of the natural phenylalanine.

b. **Tyrosine**, $C_9H_{11}NO_3$, was obtained by Liebig[37] in 1846 by fusing caseïn with potassium hydroxide; it was isolated by Schulze and Barbieri[38] from sprouts of lupines and gourds and by v. Lippmann[39] from the molasses of the sugar-beet.

[36] Fischer, B. 32, 3646; 33, 2383.
[37] Liebig, A. 57, 127.
[38] Schulze and Barbieri, B. 11, 710, 1234; 12, 1574.
[39] von Lippmann, B. 17, 2825.

It crystallizes in lustrous needles melting at 235°; it dissolves with difficulty in cold water, somewhat readily in hot; it is insoluble in ether and almost so in alcohol. In neutral and acid solutions it is lævorotatory.

Tyrosine is the para-hydroxyl-derivative of phenylalanine (*p-oxyphenylalanine*):



Tyrosine

Fused with potassium hydroxide it is decomposed into *p*-oxybenzoic acid, acetic acid, and ammonia.[40]

Erlenmeyer and Lipp synthesized it by nitrating phenylalanine, reducing the nitro-derivative with tin and hydrochloric acid and finally treating with nitrous acid the product thus obtained.

Erlenmeyer, jun., and Halsey [41] also prepared tyrosine by employing *p*-oxybenzaldehyde instead of benzaldehyde in the phenylalanine synthesis from hippuric acid and benzaldehyde.

c. **Surinamine,** $C_{10}H_{13}NO_3$, was discovered in 1824 by Hüttenschmid[42] in the bark of *Geoffroya surinamensis* Murr. (family of the Leguminosæ), and was employed as an anthelminthic. It was later extracted from other plants and described under different names, as *ratanhine,*[43] *angeline,*[44] *geoffroyine,*[45] and *andirine.*[46]

Surinamine crystallizes from hot water in needles which melt with decomposition at 257°. It is little soluble in cold water and alcohol, insoluble in ether. It possesses the character of a monacid base and of a dibasic acid. Since there are only

[40] Barth, A. 136, 110.
[41] Erlenmeyer, jun., and Halsey, B. 30, 2981; A. 307, 138.
[42] Hüttenschmid, *Magazin für Pharmacie,* 7, 287.
[43] Ruge, J. 1862, 493. Kreitmair, A. 176, 64.
[44] Peckolt, *Zeitschrift des österreichischen Apothekervereins,* 1868, 518.
[45] Winckler, *Jahrbuch der Pharmacie,* 2, 159.
[46] Hiller, A. Pharm. 230, 513.

three oxygen atoms in the molecule, the alkaloid thus probably contains a phenol group.

From its properties surinamine appears to be closely related to tyrosine; it is probably a higher homologue of the latter. Further data are, however, needed to determine its constitution.

6. Leucine.

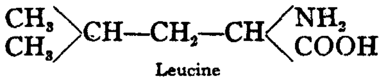
Leucine, $C_6H_{13}NO_2$, was obtained in 1818 by Proust[47] from the putrefaction of gluten and of cheese.

It is found quite widely diffused in the animal kingdom.[48] It may be prepared from caseïn by the action of trypsin and from this and other substances by hydrolytic decomposition.

It occurs also in the vegetable kingdom, as in the fungus of the fly (*Amanita muscaria* Pers.), in the sprouts of vetches, lupines, gourds, in the molasses of the sugar-beet, in potatoes, in blighted corn, etc.

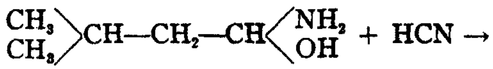
Leucine crystallizes in shining leaflets which melt at 170°. It is little soluble in cold water and alcohol, readily soluble in hot. In neutral solution it is lævo-, in acid dextrorotatory. On being heated with baryta-water to 150–160° it is converted into *inactive leucine*.[49] Nitric acid oxidizes it to oxycaproic acid, $C_5H_{10}(OH)COOH$.

Leucine is the α-amido-derivative of isocaproic or isobutylacetic acid:



Leucine

Schulze and Likiernik[50] have, indeed, synthesized inactive leucine by successively treating isovaleraldehyde-ammonia with hydrocyanic and hydrochloric acids:



Isovaleraldehyde-ammonia

[47] Proust, A. ch. [2] 10, 40.

[48] Röhmann, B. 30, 1978.

[49] Schulze, *Zeitschrift für physiologische Chemie*, 9, 108; 10, 135.

[50] Schulze and Likiernik, B. 24, 669; 25, 56.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CH_2{-}CH\!<\!\begin{matrix}NH_2\\CN\end{matrix} + H_2O.$$

α-Amido-isobutylaceto-nitrile

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CH_2{-}CH\!<\!\begin{matrix}NH_2\\CN\end{matrix} + 2H_2O \rightarrow$$

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CH_2{-}CH\!<\!\begin{matrix}NH_2\\COOH\end{matrix} + NH_3.$$

Leucine

It has also been synthesized by Erlenmeyer, jun., and Kunlin[51] from isobutyraldehyde and hippuric acid.

Under the influence of *Penicillium glaucum,* inactive leucine gives rise to the dextro-modification. The separation of inactive leucine into *d*- and *l*-leucine was effected by Fischer[52] through the cinchonine salt of the benzoyl derivative. The *l*-leucine thus obtained is identical with the natural product.

An isomeric leucine,

$$\begin{matrix}C_2H_5\\CH_3\end{matrix}\!\!>CH{-}CH\!<\!\begin{matrix}NH_2\\COOH\end{matrix}$$

has been prepared by Etard and Vila[53] from methylethylacetaldehyde-ammonia. This resembles the natural leucine, but unlike the latter it possesses an intensely sweet taste and is rather soluble in water.

7. Arginine.

Arginine, $C_6H_{14}N_4O_2$, was found by Schulze and Steiger[54] in the young shoots of gourds and lupines, particularly in the latter. It has also been noted in beet-root[55] and in several conifers. It further occurs as a decomposition-product of animal albuminoid substances.

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[51] Erlenmeyer, jun., and Kunlin, A. 316, 145.

[52] Fischer, B. 33, 2370.

[53] Etard and Vila, C. r. 134, 122.

[54] Schulze and Steiger, B. 19, 1177. Schulze, B. 24, 1098.

[55] von Lippmann, B. 29, 2645.

The salt solutions of arginine are dextrorotatory; they are without particular physiological action.

With nitrous acid arginine yields nitrogen. This indicates a primary base. When heated with baryta-water, arginine is decomposed into ammonia, urea, and *ornithine*, $C_5H_{12}N_2O_2$.[56]

According to the investigations of Ellinger[57] ornithine is *αδ-diamidovaleric acid*, $NH_2CH_2{-}CH_2{-}CH_2{-}CH(NH_2){-}COOH$, since the action of bacteria decomposes it into carbon dioxide and *tetramethylene diamine* (*putrescin*):

$$\underset{\text{Ornithine}}{(NH_2)CH_2{-}CH_2{-}CH_2{-}CH(NH_2){-}COOH} \rightarrow$$

$$CO_2 + \underset{\text{Tetramethylene diamine}}{(NH_2)CH_2{-}CH_2{-}CH_2{-}CH_2(NH_2)}.$$

This constitution is confirmed by the following synthesis of E. Fischer:[58]

By the action of bromine on γ-phthalimidopropylmalonic ester there is formed the corresponding brom-derivative:

$$\underset{\gamma\text{-Phthalimidopropylmalonic ester}}{C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle N{-}CH_2{-}CH_2{-}CH_2{-}CH\left\langle\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}\right.} + Br_2 \rightarrow$$

$$\underset{\gamma\text{-Phthalimidopropylbrommalonic ester}}{C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle N{-}CH_2{-}CH_2{-}CH_2{-}CBr\left\langle\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}\right.} + HBr.$$

Saponification of this ester and elimination of carbon dioxide from the resulting acid give *δ-phthalimido-α-bromvaleric acid*, $C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle N{-}CH_2{-}CH_2{-}CH_2{-}CHBr{-}COOH$. By treating the latter with aqueous ammonia, Br is replaced by NH_2.

[56] Schulze and Likiernik, B. 24, 2701. Schulze and Winterstein, B. 30, 2880; 32, 3191.

[57] Ellinger, B. 31, 3183; 32, 3542.

[58] Fischer, *Sitzungsber. Kgl. pr. Akad. Wiss. Berlin*, 1900, 1111.

Subsequent heating with hydrochloric acid gives rise to *αδ-diamidovaleric acid* (*ornithine*):

$$C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle N—CH_2—CH_2—CH_2—CH(NH_2)—COOH + 2H_2O \rightarrow$$

δ-Phthalimido-α-amidovaleric acid

$$C_6H_4(COOH)_2 + (NH_2)CH_2—CH_2—CH_2—CH(NH_2)—COOH.$$

Ornithine

The probable constitution of arginine is shown by its synthesis from the action of cyanamide on ornithine. The reaction takes place in aqueous solution at the ordinary temperature:

$$CNNH_2 + (NH_2)CH_2—CH_2—CH_2—CH(NH_2)—COOH \rightarrow$$

Cyanamide Ornithine

$$C\begin{cases}NH_2\\=NH\\NH—CH_2—CH_2—CH_2—CH(NH_2)—COOH.\end{cases}$$

Arginine

It is, however, not quite certain whether the cyanamide adds itself to the ω-NH_2 group as here represented or to the α-NH_2 group. According to this formula arginine must be regarded as a guanidine derivative. In full conformity with this constitution are the products obtained by oxidizing arginine with barium permanganate. There are thus formed guanidine, γ-guanidine-butyric acid, and succinic acid.[59]

d-Arginine when heated with concentrated sulphuric acid is converted into the inactive modification.[60]

8. Lysine.

Lysine, $C_6H_{14}N_2O_2$, was first obtained by Drechsel[61] from the action of hot hydrochloric acid and stannous chloride on

[59] Kutscher, *Zeitschrift für physiologische Chemie*, 32, 413.
[60] *Ibid.*, 32, 476.
[61] Drechsel, B. 25, 2455.

caseïn. It results from the decomposition with hydrochloric acid of proteïds from the seeds of conifers.[62] It occurs in the young sprouts of *Lupinus luteus*.[63]

From its yielding pentamethylene diamine (*cadaverine*) on decomposition with putrefaction bacilli, lysine appears to be *αε-diamidocaproic acid:*[64]

$$NH_2—CH_2—CH_2—CH_2—CH_2—CH(NH_2)—COOH.$$

This constitution is confirmed by the following synthesis of Fischer and Weigert:[65]

γ-Cyanpropylmalonic ester,

$$CN—CH_2—CH_2—CH_2—CH\begin{matrix}\diagup COOC_2H_5\\ \diagdown COOC_2H_5\end{matrix}$$

on treatment with nitrous acid yields *α-oximido-δ-cyanvaleric ester:*

$$CN—CH_2—CH_2—CH_2—C(NOH)—COOC_2H_5.$$

Reduction with sodium and alcohol converts the latter into lysine:

$$NH_2—CH_2—CH_2—CH_2—CH_2—CH(NH_2)—COOH.$$

The artificial lysine differs from the natural only in being optically inactive; when warmed with hydrochloric acid to 165–170°, however, the latter is converted into the inactive modification.

9. Histidine.

Histidine, $C_6H_9N_3O_2$, was obtained by Kossel[66] from the decomposition-products of a protamine. It is also formed by

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[62] Schulze and Winterstein, *Zeitschrift für physiologische Chemie*, 28, 458.
[63] Schulze, *ibid.*, 28, 465.
[64] Ellinger, B. 32, 3542.
[65] Fischer and Weigert, B. 35, 3772.
[66] Kossel, *Zeitschrift für physiologische Chemie*, 22, 181.

boiling albuminous substances with hydrochloric acid.[67] It results together with lysine from the decomposition of proteïds from the seeds of conifers.[62] It occurs in the young sprouts of *Lupinus luteus* [63] and *Lupinus albus*.[68]

Histidine crystallizes in leaflets which are readily soluble in water, little soluble in alcohol. The free base is lævo-, its hydrochloride dextrorotatory.[69]

Histidine contains an amide and a carboxyl group; little, however, is as yet known regarding its constitution.[70] It is probably a member of the asparagine group.

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[67] Hedin, *Zeitschrift für physiologische Chemie*, **22**, 191.

[68] Wassilieff, *Chemisches Centralblatt*, 1901, I, 786.

[69] Kossel and Kutscher, *Zeitschrift für physiologische Chemie*, **28**, 382.

[70] Herzog, *Zeitschrift für physiologische Chemie*, **37**, 248. Weigert, *ibid.*, **39**, 213. Fränkel, M. **24**, 229.

CHAPTER XXXVI.

THE CHOLINE GROUP.

THIS group includes three alkaloids, all of which are closely related in constitution.

1. Choline.................. $C_5H_{15}NO_2$.
2. Muscarine................ $C_5H_{15}NO_3$.
3. Betaïne.................. $C_5H_{13}NO_3$.

1. CHOLINE.

Choline (*sincaline, bilineurine, amanitine*) was obtained by Babo and Hirschbrunn[1] in 1851 by the decomposition of sinapine with barium hydroxide and was described by them under the name of sincaline.

In 1875 Schmiedeberg and Harnack[2] found choline in toadstool (*Amanita muscaria* Pers.) and gave it the name *amanitine;* it occurs in this fungus together with muscarine.

Its name, choline, was given by Strecker,[3] who isolated the base from animal gall (χολή). Of all the alkaloids choline is found most widely distributed throughout the vegetable kingdom; it is formed indifferently in the most varied plant species which bear no botanical relation to one another. It is probable that it is a product constantly occurring in the vital processes of the plant and necessary in the building up of the plant-cells.

Choline has been observed in the seeds of the pea, oat, sesame, hemp, lupine, barley, gourd, vetch, lentil, bean, cotton-plant, and goat's horn; in the fruit of the common beech, in the betel-

[1] Babo and Hirschbrunn, A. 84, 10.
[2] Schmiedeberg and Harnack, *Chemisches Centralblatt,* 1875, 629.
[3] Strecker, A. 123, 353; 148, 76.

nut, in bitter almonds, in potatoes, beets, in morels and other fungi, in the roots of the ipecacuanha, of the calamus, in the leaves of the belladonna, henbane, clover, in tea, etc.; it has also been noted in wine and beer.

Choline is also found, as has been indicated, in the animal organism. Liebreich obtained it in 1865 by treating the brain of an ox with barium hydroxide. It is ordinarily prepared by boiling the yolk of the egg with baryta-water.

These different animal and plant products contain choline not originally as such, but in the form of complicated derivatives which are known as *lecithins*—basic bodies soluble in water, alcohol, and ether.

By the action of acids or of alkalies the lecithins are decomposed into choline, glycerine, phosphoric acid, and higher fatty acids. Because of this decomposition they are represented by the following general formula:

$$C_3H_5\left\langle\begin{array}{l} O-R \\ O-R' \\ O-PO\left\langle\begin{array}{l} OH \\ O-C_5H_{14}NO \end{array}\right. \end{array}\right.$$

in which R and R′ designate the radicals of stearic, palmitic, or oleïc acid.

The lecithins play an important rôle in the plant organism. They appear to be closely related to the chlorophyll; it is possible, indeed, that chlorophyll itself is to be classed among these substances and that their formation is due to its decomposition. This view, however, is at present largely speculative.

Choline forms a non-crystallizable sirup which deliquesces in the air and dissolves in water in all proportions. It is strongly alkaline in reaction; physiologically its action is slight.

It is a quaternary base of the ammonium type; its nitrogen atom is pentatomic with one of its valences attached to a hydroxyl group. Its salts are formed with the elimination of water, the hydroxyl being replaced by an acid radical:

$$\underset{\text{Choline}}{C_5H_{14}\equiv N{-}OH} + HCl \rightarrow \underset{\text{Choline hydrochloride}}{C_5H_{14}\equiv N{-}Cl} + H_2O.$$

Choline is trimethyl oxyethyl ammonium hydroxide:

$$\underset{\text{Choline}}{(CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2-OH}_{OH}}$$

Its constitution is established by the following syntheses:

1′. Choline hydrochloride is formed when trimethylamine is heated with glycol chlorhydrin:[4]

$$\underset{\text{Trimethylamine}}{(CH_3)_3\equiv N} + \underset{\text{Glycol chlorhydrin}}{CH_2Cl-CH_2OH} \rightarrow \underset{\text{Choline hydrochloride}}{(CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2-OH}_{Cl}}$$

2′. Choline itself results from the action of ethylene oxide on an aqueous solution of trimethylamine at the ordinary temperature:[4]

$$\underset{\text{Trimethylamine}}{(CH_3)_3\equiv N} + \underset{\text{Ethylene oxide}}{\underset{\diagdown O \diagup}{CH_2-CH_2}} + H_2O \rightarrow \underset{\text{Choline}}{(CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2-OH}_{OH}}$$

3′. If ethylene bromide acts upon trimethylamine and the resulting addition-product, ***bromethyl trimethyl ammonium bromide***, is treated with silver nitrate, choline nitrate is formed:[5]

$$(CH_3)_3\equiv N + CH_2Br-CH_2Br \rightarrow (CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2Br}_{Br}$$

$$(CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2Br}_{Br} + 2AgNO_3 + H_2O \rightarrow$$

$$(CH_3)_3\equiv N\Big\langle{}^{CH_2-CH_2-OH}_{NO_3} + 2AgBr + HNO_3.$$

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[4] Würtz, C. r. 65, 1015.

[5] Bode, A. 267, 271; A. Pharm. 229, 469.

The constitution of choline also follows from its decomposition-products; when a concentrated aqueous solution of choline is boiled, the base is decomposed into trimethylamine and glycol.

Choline is of particular interest because of its relation to the opium alkaloids. Thus morphine when decomposed yields a base, dimethyl-oxyethylamine, $(CH_3)_2N—CH_2—CH_2—OH$, which with methyl iodide gives the hydriodide of choline. From this morphine as well as codeïne and thebaïne appear to be choline derivatives (page 277).

Choline hydrochloride with acetyl and benzoyl chlorides forms acetyl and benzoyl derivatives (proof of the hydroxyl group).[6]

When this same hydrochloride is heated with hydriodic acid to 120–150°, the iodide $(CH_3)_3{\equiv}NI—CH_2—CH_2I$, is obtained. Moist silver oxide transforms this derivative into trimethyl vinyl ammonium hydroxide:

$$(CH_3)_3{\equiv}N\begin{cases}CH{=}CH_2\\OH\end{cases}$$

This last substance is identical with ***neurine***, an extremely poisonous base, which was discovered in 1865 by Liebreich at the same time as choline on treating ox-brain with baryta-water.[7]

By the action of oxidizing agents (nitric acid, chromic acid, potassium permanganate) choline is changed to betaïne.

2. MUSCARINE.

This base is the poisonous principle of the mushroom (*Amanita muscaria* Pers.). It was isolated from this by Schmiedeberg and Koppe[8] in 1870. It is also found in some other poisonous

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[6] Bayer, A. 142, 325.
[7] *Ibid.*, 140, 311.
[8] Schmiedeberg and Koppe, B. 3, 281.

fungi, to which possibly it imparts the poisonous character; also, according to Marino-Zucco and Vignolo,[9] in the flowers and fruit of *Cannabis indica*, family of the Cannabinaceæ.

It forms deliquescent crystals which are quite soluble in water and alcohol, insoluble in ether. It is a strong base without odor or taste and is highly poisonous. When heated it is decomposed, trimethylamine being formed.

Muscarine like choline then is to be regarded as an ammonium hydroxide; in the formation of its salts a hydroxyl group is replaced by an acid radical:

$$\underset{\text{Muscarine}}{C_5H_{14}O_2\equiv N{-}OH} + HCl \rightarrow \underset{\text{Muscarine hydrochloride}}{C_5H_{14}O_2\equiv N{-}Cl} + H_2O.$$

The constitution of muscarine has not as yet been fully determined. Until recent years it was regarded as acetal trimethyl ammonium hydroxide:

$$(CH_3)_3\equiv N\begin{cases} CH_2{-}CH(OH)_2 \\ OH \end{cases}$$

Attempts to synthesize muscarine, however, have cast some doubt on the above constitution. Fischer,[10] by methylating acetal-amine and Berlinerblau [11] from trimethylamine and chloracetal, obtained bases mutually identical but different from the natural muscarine. Fischer further showed that the snythesized base possessed the constitution represented, since oxidation with silver oxide converted it into betaïne:

$$(CH_3)_3\equiv N\begin{cases} CH_2{-}CH_2{-}OH \\ OH \end{cases} + 2O \rightarrow$$

$$\underset{\text{Betaïne}}{(CH_3)_3\equiv N\begin{cases} CH_2{-}COOH \\ OH \end{cases}} + H_2O.$$

[9] Marino-Zucco and Vignolo, G. 25, 262.
[10] E. Fischer, B. 26, 468; 27, 165.
[11] Berlinerblau, B. 17, 1139.

On the other hand, in favor of the above constitution for muscarine is the statement of Schmiedeberg and Harnack [12] that muscarine is formed by the oxidation of choline with nitric acid:

$$(CH_3)_3{\equiv}N{<}^{CH_2-CH_2-OH}_{OH} + O \rightarrow$$

Choline

$$(CH_3)_3{\equiv}N{<}^{CH_2-CH(OH)_2}_{OH}$$

Muscarine (?)

The product thus obtained, indeed, closely resembles the natural muscarine, but, as careful study has shown, it is not identical with the latter.[13]

An isomuscarine,

$$(CH_3)_3{\equiv}N{<}^{CH(OH)-CH_2OH}_{OH}$$

has been prepared by Bode.[14]

3. Betaïne.

Betaïne was discovered by Scheibler [15] in 1869 in beet-root (*Beta vulgaris* L., family of the Chenopodiaceæ), where it is found associated with a large number of other organic substances, such as malic, tartaric, oxalic, citric, aconitic, tricarballylic, aspartic acids, and such bases as choline, xanthine, hypoxanthine, guanine, asparagine, etc. In unripe beets its quantity amounts to about 0.25%, in the ripe it decreases to 0.1%; in the molasses the base is found in much larger quantity, often as high as 3%.

Betaïne occurs also in other plants, accompanied ordinarily by choline and trigonelline. It has been obtained from cotton-

[12] Schmiedeberg and Harnack, *Archiv für experimentelle Pathologie*, 6, 101; J. 1876, 804.

[13] Nothnagel, B. 26, 801.

[14] Bode, A. 267, 291.

[15] Scheibler, B. 2, 292; 3, 155; *Zeitschrift für Chemie*, 9, 279.

seed, from the barley, the vetch, from ***Chenopodium album*** L., *Artemisia Cina* Berg., *Lycium barbarum* L., *Scopolia atropoides* Bercht., from the leaves of the potato, and from the root of *Althæa officinalis.*

Emmerling[16] noted its occurrence among the products resulting from the putrefaction of gluten.

It crystallizes from alcohol in large, hygroscopic crystals which are sweet and refreshing to the taste. It is readily soluble in water and alcohol, insoluble in ether.

Betaïne is a weak base, neutral in reaction, optically inactive, and non-poisonous.

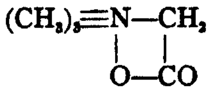
Like choline and muscarine it is a quaternary ammonium base:

$$\underset{\text{Betaïne}}{C_5H_{12}O_2{\equiv}N{-}OH} \qquad \underset{\text{Betaïne hydrochloride}}{C_5H_{12}O_2{\equiv}N{-}Cl}$$

The constitution of betaïne is shown by its different syntheses. It is the methyl hydroxide of *dimethylglycocoll:*

$$(CH_3)_3{\equiv}N\begin{matrix}\diagup CH_2{-}COOH\\ \diagdown OH\end{matrix}$$

Betaïne easily loses the elements of a molecule of water; to effect this it suffices to heat the substance to 100° or simply to let it stand over sulphuric acid. The resulting anhydride (melting-point 150°),



is the prototype of the so-called organic ***betaïnes.***

Betaïne may be prepared:

1′. By the oxidation of choline with chromic acid or potassium permanganate:[17]

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[16] Emmerling, B. 29, 2721.
[17] Liebreich, B. 2, 12, 167; 3, 761.

$$\underset{\text{Choline}}{(CH_3)_3N\left\langle\begin{matrix}CH_2\text{—}CH_2OH\\OH\end{matrix}\right.} + 2O \rightarrow \underset{\text{Betaïne}}{(CH_3)_3N\left\langle\begin{matrix}CH_2\text{—}COOH\\OH\end{matrix}\right.} + H_2O$$

2′. By the condensation of trimethylamine with monochloracetic acid:[17]

$$\underset{\text{Trimethylamine}}{(CH_3)_3N} + \underset{\text{Chloracetic acid}}{CH_2Cl\text{—}COOH} \rightarrow \underset{\text{Betaïne hydrochloride}}{(CH_3)_3N\left\langle\begin{matrix}CH_2\text{—}COOH\\Cl\end{matrix}\right.}$$

3′. By the action of methyl iodide on glycocoll in the presence of an alkali:[18]

$$\underset{\text{Glycocoll}}{NH_2\text{—}CH_2\text{—}COOH} + 3CH_3I + 3KOH \rightarrow$$

$$\underset{\text{Betaïne}}{(CH_3)_3N\left\langle\begin{matrix}CH_2\text{—}COOH\\OH\end{matrix}\right.} + 3KI + 2H_2O$$

Sarcosine, $C_3H_7NO_2$.—Sarcosine, which was discovered by Liebig[19] in 1847 in the decomposition-products of creatine, is closely related to betaïne. It has been obtained by Rosengarten and Strecker[20] by boiling caffeïne with baryta-water. It crystallizes in rhombic prisms which dissolve readily in water but with difficulty in alcohol; it tastes sweet and melts with decomposition at 210–215°.

Sarcosine is methylglycocoll (methylamidoacetic acid):

$$\underset{\text{Sarcosine}}{CH_3NH\text{—}CH_2\text{—}COOH.}$$

Its constitution is indicated by its synthesis from methylamine and chloracetic acid.[21]

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[18] Griess, B. 8, 1406.
[19] Liebig, A. 62, 310.
[20] Rosengarten and Strecker, A. 157, 1.
[21] Volhard, A. 123, 261.

The relation between sarcosine and betaïne is shown in the following formulæ:

$$\begin{array}{l} CH_2\text{—}NHCH_3 \\ | \\ COOH \end{array} \qquad \begin{array}{l} CH_2\text{—}N(CH_3)_2\left\langle\begin{array}{l} CH_3 \\ OH \end{array}\right. \\ | \\ COOH \end{array}$$

Sarcosine (Methylglycocoll) — Betaïne (Dimethylglycocoll methyl hydroxide)

CHAPTER XXXVII.

ALKALOIDS OF THE MUSTARD-SEED.

THE seeds of the mustard, *Sinapis alba* L. and *Sinapis nigra* L. (family of the Cruciferæ), contain two alkaloids:

Sinapine. . . . . $C_{16}H_{25}NO_6$
Sinalbin. . . . . $C_{30}H_{42}N_2S_2O_{15}$

The former is found in black mustard, the latter in white. In black mustard there occurs furthermore a glucoside, the potassium salt of myronic acid, $C_{10}H_{16}NS_2KO_9+H_2O$. When saponified this yields glucose, allyl mustard-oil, and potassium bisulphate.

1. SINAPINE.

Sinapine was discovered by Henry and Garot[1] in 1825. It is obtained in the form of its difficultly soluble sulphocyanate $C_{16}H_{24}NO_5 \cdot SCN + H_2O$ by adding potassium sulphocyanate to an alcoholic extract of mustard-seed. Sinapine also results from the decomposition of sinalbin.[2]

According to Gadamer[3] sinapine occurs in black mustard but not in white; the latter contains only sinalbin, which in its decomposition yields sinapine.

Sinapine is not known in the free state. If we attempt to isolate it from any of its salts, we obtain a deep yellow solution of strongly alkaline reaction. When, however, the solvent is driven off, the alkaloid suffers decomposition.

This decomposition takes place still more readily if the aqueous

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[1] Henry and Garot, *Journal de pharmacie*, [2] 20, 63; 42, 1.
[2] Will and Laubenheimer, A. 199, 150.
[3] Gadamer, A. Pharm. 235, 44, 81; B. 30, 2322, 2330.

solution is heated with an alkali; there are thus formed ***choline*** and ***sinapic acid:***[4]

$$\underset{\text{Sinapine}}{C_{16}H_{25}NO_6} + H_2O \rightarrow \underset{\text{Choline}}{C_5H_{15}NO_2} + \underset{\text{Sinapic acid}}{C_{11}H_{12}O_5}.$$

The constitution of choline we have already learned (page 472); that of sinapic acid was studied by Remsen and Coale[5] and later by Gadamer.

Sinapic acid crystallizes from alcohol in prisms which melt at 191–192°; at a higher temperature the acid is decomposed. It is little soluble in cold alcohol and still less in water and ether. It is a monobasic acid; treated with alcohol and hydrochloric acid it yields an ester.

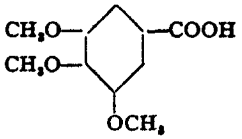
It contains two methoxyls (method of Zeisel) and one hydroxyl (acetyl derivative). When treated with methyl iodide in alkaline solution it yields the methyl ester of *methylsinapic acid* (melting-point 91°):

$$\underset{\text{Sinapic acid}}{C_8H_4(OCH_3)_2(OH)(COOH)} + 2NaOH + 2CH_3I \rightarrow$$

$$\underset{\text{Methylsinapic methyl ester}}{C_8H_4(OCH_3)_3COOCH_3} + 2NaI + 2H_2O.$$

By the saponification of this ester with alcoholic potash the free methylsinapic acid, $C_8H_4(OCH_3)_3COOH$, is obtained (needles melting at 124°).

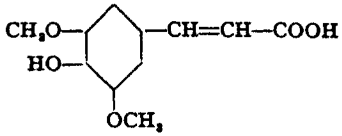
On oxidizing methylsinapic acid with potassium permanganate in alkaline solution, Gadamer obtained *trimethylgallic acid:*



[4] Babo and Hirschbrunn, A. 84, 10.

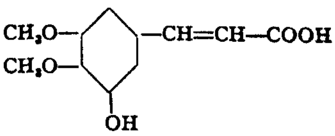
[5] Remsen and Coale, Am. Chem. Jour. 6, 50.

From this may be deduced either of the two following formulæ for sinapic acid:



I

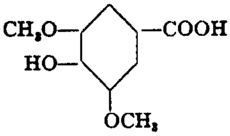
or



II

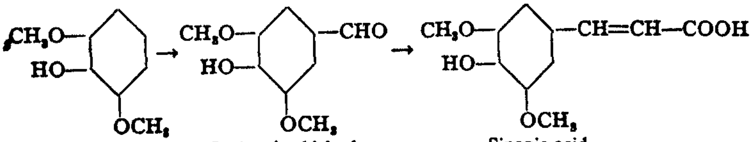
To determine which of these represents the acid, Gadamer prepared its acetyl derivative and oxidized this with potassium permanganate.

On saponifying the oxidation-product he obtained a dimethyl-gallic acid which proved to be identical with syringaic acid (melting-point 202°), whose constitution had already been shown by Koerner[6] to be



Consequently the constitution of sinapic acid is expressed by formula I.

This constitution has been recently confirmed by the synthesis of sinapic acid from the dimethyl ether of pyrogallol.[7] By the action of chloroform and caustic soda on the latter (reaction of Reimer-Tiemann) it is converted into syringaic aldehyde. If this aldehyde is now condensed with sodium acetate and acetic anhydride, sinapic acid is formed. The course of the reaction may be formulated as follows:



Dimethyl ether of pyrogallol — Syringaic aldehyde — Sinapic acid

[6] Koerner, G. 18, 209.

[7] Gruebe and Martz, B. 36, 215, 1031.

Now, sinapine is the product representing the union of sinapic acid and choline with the elimination of one molecule of water; it is, furthermore, a quaternary base. Its constitution must, therefore, be expressed by the following formula:

$$\begin{matrix} HO \\ (CH_3O)_2 \end{matrix}\!\!>\!C_6H_2{-}CH{=}CH{-}CO{-}O{-}CH_2{-}CH_2{-}N\!\begin{matrix} \equiv(CH_3)_3 \\ \diagdown OH \end{matrix}$$

Sinapine

2. SINALBIN.

Sinalbin was discovered in white mustard by Will and Laubenheimer in 1879. It crystallizes from dilute alcohol in prismatic needles which contain five molecules of water of crystallization and which melt at 83–84°; in the anhydrous condition it melts at 139–140°. It is little soluble in water and cold alcohol, insoluble in ether. Its aqueous solutions react alkaline, taste very bitter, and are lævorotatory. Alkalies color them a deep yellow.

Sinalbin is a glucoside; it is readily decomposed by different agents, particularly by *myrosin*, a ferment which is found in the mustard-seed. Sinalbin is thus decomposed into dextrose, sinapine sulphate, and a substance, C_8H_7NSO, which proves to be *sinalbin mustard-oil:*

$$\underset{\text{Sinalbin}}{C_{30}H_{42}N_2S_2O_{15}} + H_2O \rightarrow$$

$$\underset{\text{Dextrose}}{C_6H_{12}O_6} + \underset{\text{Sinapine bisulphate}}{C_{16}H_{24}NO_5 \cdot HSO_4} + \underset{\text{Sinalbin mustard-oil}}{C_8H_7NSO}.$$

This decomposition of sinalbin under the action of myrosin is effected by simply allowing powdered mustard-seeds to stand in contact with water.

The derivative, C_8H_7NSO, is a yellow oil possessing a very sharp taste and acting upon the skin as a strong irritant. It is almost insoluble in water, but dissolves readily in alcohol, ether, and in alkalies.

Its constitution was pointed out by Salkowski.[8] This investigator found that the derivative was identical with *p-oxybenzyl isosulphocyanate*, $C_6H_4\left\langle\begin{matrix}CH_2\text{—}NCS(1)\\ OH(4)\end{matrix}\right.$, which he obtained by treating *p*-oxybenzylamine with carbon bisulphide.

With mercuric chloride or sulphate or silver nitrate, sinalbin forms white precipitates. When these are treated with hydrogen sulphide a decomposition ensues which resembles that resulting from the action of myrosin on sinalbin:

$$\underset{\text{Sinalbin}}{C_{30}H_{42}N_2S_2O_{15}} + H_2O \rightarrow$$

$$\underset{\text{Dextrose}}{C_6H_{12}O_6} + \underset{\text{Sinapine bisulphate}}{C_{16}H_{24}NO_5 \cdot HSO_4} + C_8H_7NO + S.$$

The body, C_8H_7NO (melting-point 69°), yields on saponification ammonia and *p-oxyphenylacetic acid*, $C_8H_8O_3$. It is accordingly the nitrile of the latter acid:

$$C_6H_4\left\langle\begin{matrix}CH_2\text{—}CN(1)\\ OH(4)\end{matrix}\right.$$

From these considerations the following constitution has been assigned to sinalbin:

$$C\left\langle\begin{matrix}O\text{—}SO_2\text{—}O\text{—}N(CH_3)_3\text{—}CH_2\text{—}CH_2\text{—}O\text{—}CO\text{—}CH{=}CH\text{—}C_6H_2(OCH_3)_2OH\\ S\text{—}C_6H_{11}O_5\\ N\text{—}\underset{(1)}{CH_2}\text{—}C_6H_4\text{—}\underset{(4)}{OH}\end{matrix}\right.$$

[8] Salkowski, B. 22, 2137.

CHAPTER XXXVIII.

TRIMETHYLAMINE.

LIKE the bases of the choline group trimethylamine does not appear to be a product of assimilation in the vital processes of the plant, but results rather from the decomposition of more complex substances, such as the lecithins and choline.

Trimethylamine has been observed in a large number of plants. It was discovered in the leaves of *Chenopodium vulvaria* L. (family of the Chenopodiaceæ) by Dessaignes [1] in 1851. Later it was found in the blossoms of the hawthorn, mountain-ash, wild-brier, and pear-tree, in the seed of the beech-tree, in *Arnica montana* L., in *Mercurialis annua*, in ergot, in the toadstool, in beet-root, etc.

It is obtained from these plants by simply distilling them with water and alkali. One might possibly infer that the trimethylamine is formed during this process from the immediate decomposition of more complex basic derivatives. This, however, is not the case; from investigations of Wicke [2] trimethylamine is shown to be present as such in the plant.

The same year in which trimethylamine was discovered it was synthesized by Hofmann [3] by the action of methyl iodide on ammonia.

Trimethylamine is a strong base (boiling-point 3.5°). It dissolves in water, alcohol, and ether in all proportions, and possesses a disagreeable fish-like odor.

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[1] Dessaignes, C. r. **33**, 358; **43**, 670.
[2] Wicke, A. **91**, 121; **124**, 338.
[3] Hofmann, A. **79**, 11; **83**, 116.

Alkylamines other than trimethylamine are seldom met with in plants.

Dimethylamine has been noted in decayed mushrooms, *methylamine* in the molasses of the sugar-beet and in *Mercurialis annua*,[4] *ethylamine* has been found in spoiled wheaten flour, and *propylamine* has been detected in ergot.[5]

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[4] Schmidt, A. 193, 73.
[5] Wenzell, J. 1864, 14.

CHAPTER XXXIX.

ALKALOIDS OF UNKNOWN CONSTITUTION.

Of the remaining alkaloids whose empirical formula may be regarded as fairly well established, but whose constitution is as yet unknown, we shall mention the following:

1. **Stachydrine,** $C_7H_{13}NO_2+H_2O$.—In the tubercles of *Stachys tuberifera* Bunge (Labiatæ); in the leaves of *Citrus Aurantium* L. Deliquescent crystals, quite soluble in water. Melting-point 210°. Contains a carboxyl and two *n*-methyls. Is decomposed by very concentrated alkali, dimethylamine being evolved.

2. **Alkaloids from the Leaves of** *Ephedra vulgaris* Rich. (Coniferæ):

Ephedrine, $C_{10}H_{15}NO$. Crystals; boils without decomposition at 255°. A secondary base. When heated with gold chloride in aqueous solution it yields methylamine and benzaldehyde. From *Ephedra monostachia* an alkaloid, $C_{13}H_{19}NO$, has been isolated, which also bears the name ephedrine; this forms crystals melting at 112°.

Pseudoephedrine, $C_{10}H_{15}NO$. Crystals, melting at 114–115°. A secondary base, bitter in taste. Contains a hydroxyl. On oxidation with potassium permanganate yields benzoic acid. The action of concentrated hydrochloric acid at 180° gives rise to methylamine and an oil, which on oxidation is converted into benzoic acid.

3. **Damascenine,** $C_9H_{11}NO_3$.—In the seeds of *Nigella Damascena* L. (Ranunculaceæ). Prisms. Melting-point 27°. Boiling-point 168°. Contains two methoxyl groups. Its salts fluoresce.

4. **Jambosine,** $C_{10}H_{15}NO_3$.—In the bark of *Myrtus Jambosa* (Myrtaceæ). Crystals, melting at 77°; soluble in alkalies.

5. Alkaloids from Cacti.—In different species of the genus *Anhalonium* (family of the Cactaceæ) are found the following alkaloids, which in the plant are in combination with malic acid:

a. Anhaline, $C_{10}H_{17}NO_2$. Prisms. Melting-point 115°.

b. Mezcaline, $C_{11}H_{17}NO_3$. Needles, melting at 151°; soluble in water. Contains three methoxyls and a *n*-methyl. A strong tertiary base.

c. Anhalonidine, $C_{12}H_{15}NO_5$. Needles, melting at 160°; readily soluble in water. Contains two methoxyls, but neither hydroxyl nor *n*-methyl. Inactive. Its salts are dextrorotatory.

d. Anhalonine, $C_{12}H_{15}NO_3$. Secondary base. Needles. Melting-point 85°. Boils without decomposition. Contains a methoxyl but no hydroxyl. Its salts are lævorotatory.

e. Lophophorine, $C_{13}H_{17}NO_3$. An oil. Inactive. Contains a methoxyl but no *n*-methyl. Very poisonous.

f. Pellotine, $C_{13}H_{19}NO_3$. Plates, melting at 110°; insoluble in water, soluble in organic solvents. A tertiary base. Acts as a narcotic. Contains a hydroxyl, a *n*-methyl, and two methoxyls. On distillation over zinc-dust or soda-lime yields trimethylamine.

6. Carpaïne, $C_{14}H_{25}NO_2$.—In the leaves of *Carica Papaya* L. (Passifloraceæ). Rhombic prisms, melting at 121°. May be sublimed. Insoluble in alkalies. A secondary base, dextrorotatory. Contains a hydroxyl.

7. Chrysanthemine, $C_{14}H_{28}N_2O_3$.—In the blossoms of *Chrysanthemum cinerariæfolium* Vis. (Compositæ). Deliquescent needles. Diacid base. Inactive. Contains one hydroxyl and one NH group. On distillation over soda-lime, trimethylamine and a pyridine base are formed. Oxidation gives rise to trimethylamine and succinic acid. Heated with caustic potash chrysanthemine is decomposed into trimethylamine, γ-oxybutyric acid and an acid, $C_5H_{10}N$—COOH (*piperidine carboxylic acid*); heated with concentrated hydriodic acid it yields alkyl iodides and a methylpiperidine carboxylic acid. Under the action of superheated steam piperidine derivatives are also formed.

8. Caffearine, $C_{14}H_{16}N_2O_4$.—In coffee (*Coffea arabica* L., family of the Rubiaceæ). Deliquescent needles, very soluble in

water. Melting-point 140°. Monacid base, inactive. In physiological action, a narcotic.

9. **Eserine** (*physostigmine*), $C_{15}H_{21}N_3O_2$.—In Calabar beans, the seed of *Physostigma venenosum* Balf. (Leguminosæ). Prisms. Melting-point 105–106°. Tertiary, monacid base, in reaction alkaline. Lævorotatory. Extremely poisonous. Causes contraction of the pupil. Contains a hydroxyl and two *n*-methyls. When boiled with potassium hydroxide or distilled over zinc-dust yields methylamine.

10. **Matrine,** $C_{15}H_{24}N_2O$.—In the root of *Sophora angustifolia* Sieb. (Leguminosæ). Melting-point 80°. Dextrorotatory. Readily soluble in water.

11. **Piliganine,** $C_{15}H_{24}N_2O$.—In *Lycopodium Saururus* Lam. (Lycopodiaceæ). Needles, melting at 64–65°; readily soluble in water. Very poisonous. Acts as a purgative and an emetic.

12. **Piperovatine,** $C_{16}H_{21}NO_2$.—In *Piper ovatum* Vahl. (Piperaceæ). Needles, melting at 123°. A very weak base, inactive, neutral in reaction. When heated with water to 160° yields a pyridine base.

13. **Paricine,** $C_{16}H_{18}N_2O$.—In the bark of *Cinchona succirubra* Pav. (Rubiaceæ), which contains furthermore the principal cinchona alkaloids. A yellow, amorphous powder. Melting-point 130°. A monacid base, inactive.

14. **Ricinine,** $C_{17}H_{18}N_4O_4$.—In the seed of *Ricinus communis* L. (Euphorbiaceæ). Plates, melting at 194°. Neutral reaction. Inactive. Is decomposed by alkali into methyl alcohol and an acid, $C_{15}H_{14}N_4O_4$.

15. **Bebeerine** (*pelosine*), $C_{18}H_{21}NO_3$.—In the bark of *Nectandra Rodiæi* Schomb., of *Hernandia sonora* L. (Lauraceæ), and of *Cissampelos Pareira* L. (Menispermaceæ). Amorphous powder, soluble in alkalies, lævorotatory. Melting-point 180°. A tertiary base. Contains a methoxyl, a *n*-methyl, and a hydroxyl, but no carboxyl. On distillation with caustic potash yields methylamine and pyrrol; with zinc-dust, *o*-cresol and methylamine. Nitric acid gives rise to nitro-derivatives. Possesses febrifugal properties.

Buxine, $C_{18}H_{21}NO_3$, which is obtained from the bark of *Buxus sempervirens* L. (Euphorbiaceæ), and which was supposed to be identical with bebeerine, appears to be a distinct alkaloid.

16. **Senecionine,** $C_{18}H_{26}NO_6$.—In groundsel (*Senecio vulgaris* L., Compositæ). Crystalline, lævorotatory.

17. **Nupharine,** $C_{18}H_{24}N_2O_2$.—In the rhizome of the water-lily (*Nuphar luteum* Sibth., Nymphæaceæ). Amorphous, inactive.

18. **Alkaloids from the Bark of** *Geissospermum Vellosii* Allem. (Apocynaceæ).—This bark has been employed as a febrifuge.

a. Pereirine, $C_{19}H_{24}N_2O$. Amorphous, monacid base. Melting-point 124°.

b. Geissospermine, $C_{19}H_{24}N_2O_2 + H_2O$. Prisms, melting at 160°. Monacid base, lævorotatory.

c. Vellosine, $C_{23}H_{28}N_2O_4$. Plates, melting at 189°. Monacid, tertiary base, dextrorotatory, very poisonous. Contains two methoxyls.

19. **Alkaloids from Angustura Bark** (*Galipea Cusparia* Rut., Rutaceæ).—This bark is also employed as a febrifuge. It contains in the free condition the following four tertiary bases, which are all crystalline:

a. Cusparine, $C_{20}H_{19}NO_3$. Melting-point 92°. Is decomposed by caustic potash into an aromatic acid and a basic body.

b. Cusparidine, $C_{19}H_{17}NO_2$. Melting-point 79°.

c. Galipine, $C_{20}H_{21}NO_3$. Melting-point 115°.

d. Galipidine, $C_{19}H_{19}NO_3$. Melting-point 110°.

20. **Achilleïne,** $C_{20}H_{38}N_2O_{15}$. In *Achillea Millefolium* L. and *A. moschata* Jacq. (Compositæ). Amorphous mass of reddish-brown color, deliquescent, soluble in water with a yellow color. When boiled with dilute sulphuric acid, is decomposed into a sugar, ammonia, a volatile aromatic substance, and an amorphous base, *achilletine*, $C_{11}H_{17}NO_4$.

21. **Alkaloids of the Celandine.**—The following Papaveraceæ—celandine (*Chelidonium majus* L.), *Sanguinaria canadensis* L., *Stylophorum diaphyllum* Nutt., *Bocconia frutescens* Wild., and

Macleya cordata R. Br.—contain in addition to protopine (page 294) the following six alkaloids, which in the plant are in combination with the acids—malic, succinic, citric, and chelidonic (page 21).

a. Chelidonine, $C_{20}H_{19}NO_5+H_2O$. Plates or needles, melting at 135–136°. Tertiary base. Colorless salts. Oxidation with potassium permanganate gives rise to oxalic acid and methylamine. Contains a hydroxyl, a *n*-methyl, but no methoxyl group. Is dextrorotatory.

b. Chelerythrine, $C_{21}H_{17}NO_4$. Crystals, melting at 203°. Its salts are yellow and exhibit a violet fluorescence. Burning to the taste; inhaled in powdered form provokes sneezing. Inactive. Contains two methoxyls.

c. Sanguinarine, $C_{20}H_{15}NO_4+H_2O$. Needles, melting at 213°. Red salts with violet fluorescence. Sharp taste. Provokes sneezing. Inactive. Contains one methoxyl.

d. α-Homochelidonine, $C_{21}H_{21}NO_5$. Melting-point 182°.

e. β-Homochelidonine, $C_{21}H_{23}NO_5$. Melting-point 159°.

f. γ-Homochelidonine, $C_{21}H_{23}NO_5$. Melting-point 169°.

The last three alkaloids are crystalline and contain two methoxyls.

Some of the alkaloids mentioned above are found in other plants than in those named, as in *Adlumia Cirrhosa* Raf. (Fumariaceæ) and in *Eschscholtzia californica.*

22. **Fumarine,** $C_{21}H_{19}NO_4$.—In *Fumaria officinalis* L. (Fumariaceæ). Prisms, melting at 199°. Optically active.

23. **Rhœadine,** $C_{21}H_{21}NO_6$.—In the poppy (*Papaver Rhœas* L., Papaveraceæ). Prisms. Melting-point 232°. Weak base. Sublimes in an atmosphere of carbon dioxide.

24. **Artarine,** $C_{21}H_{23}NO_4$.—In the bark of *Xanthoxylum Senegalense* DC. (Rutaceæ). Amorphous powder of grayish-red color; melts with decomposition at 240°. Yellow salts.

25 **Abrotine,** $C_{21}H_{22}N_2O$.—In *Artemisia Abrotanum* L. (Compositæ). Needles, readily soluble in hot water; the solution shows a blue fluorescence. Diacid base.

26. **Alkaloids of the Quebracho Barks.**—The bark of *Aspi-*

dosperma Quebracho Schlecht. (Apocynaceæ) is used as a febrifuge. It contains the following six alkaloids in combination with tannic acid:

a. Quebrachine, $C_{21}H_{26}N_2O_3$. Needles, melting at 214–216°, dextrorotatory, insoluble in water.

b. Hypoquebrachine, $C_{21}H_{26}N_2O_2$. A yellow, amorphous mass, melting near 80°.

c. Quebrachamine. Leaflets. Melting-point 142°.

d. Aspidospermine, $C_{22}H_{30}N_2O_2$. Prisms. Melting-point 205–206°. Very weak base, lævorotatory; neutral in reaction; soluble in water with difficulty. Boiled with caustic potash, is decomposed into pyridine, quinoline, and similar smelling bases.

e. Aspidospermatine, $C_{21}H_{28}N_2O_2$. Needles, somewhat soluble in water. Melting-point 162°. Lævorotatory.

f. Aspidosamine, $C_{22}H_{28}N_2O_2$. Flocculent precipitate. Melting-point near 100°.

The bark of one tree of the genus *Aspidosperma* contains *paytine*, $C_{21}H_{24}N_2O + H_2O$ (prisms, melting-point 156°, lævorotatory), and *paytamine*, $C_{21}H_{24}N_2O$ (amorphous).

The bark of *Quebracho colorado* (*Loxopterygium Lorentzii*, Griesebach, Anacardiaceæ) contains as active principal, *Loxopterygine*, $C_{26}H_{34}N_2O_2$. Amorphous; melts at 81°; is decomposed at higher temperatures, giving apparently quinoline.

All these alkaloids are monacid bases.

27. **Alkaloids of the Alstonia Barks** (Apocynaceæ).—These barks are valued for their febrifugal properties. *Alstonia constricta* Muell. contains:

a. Alstonine (*Chlorogenine*), $C_{21}H_{20}N_2O_4 + 3\frac{1}{2}H_2O$. A brown, amorphous mass, soluble in water. Melts in the anhydrous condition at about 195°.

b. Porphyrine, $C_{21}H_{25}N_3O_2$. Melting-point 97°.

The solutions of both these alkaloids show a blue fluorescence.

Alstonia spectabilis R. Br. and *A. scholaris* R. Br. contain:

c. Ditamine, $C_{16}H_{19}NO_2$. Amorphous powder. Melting-point 75°.

d. Echitamine (*ditaine*), $C_{22}H_{28}N_2O_4 + 4H_2O$. Prisms, melting

with decomposition at 206°; readily soluble in water. Lævorotatory. Strongly basic; possibly a quaternary base.

e. Echitenine, $C_{20}H_{27}NO_4$. A brown, amorphous substance.

All these alkaloids are monacid bases.

28. **Hymenodictine,** $C_{23}H_{40}N_2$.—In the bark of *Hymenodictyon excelsum* Wall. (Rubiaceæ). Needles, melting at 66°. Diacid and bitertiary base.

29. **Aribine,** $C_{23}H_{20}N_4+8H_2O$.—In the bark of *Arariba rubra* Mart. (Rubiaceæ). Prisms. Melting-point of the anhydrous base 229°. Sublimes without decomposition. A strong base, inactive, diacid, and bitertiary.

30. **Yohimbine,** $C_{23}H_{32}N_2O_4$.—In the bark and leaves of the *Yohimbé-* or *Yumbehoa*-tree (Rubiaceæ). White needles. Melting-point 234°. Dextrorotatory. Monacid, tertiary base. Contains a hydroxyl (acetyl derivative) and a methoxyl. Is the methyl ester of a carboxylic acid. Oxidation with potassium chlorate gives rise to formic acid; with potassium permanganate, to *yohimbic acid*, $C_{20}H_{24}N_2O_6$, and *noryohymbic acid*, $C_{19}H_{20}N_2O_7$. Phenylhydrazine is without action.

The salts of yohimbine are formed with the elimination of a molecule of water.

With yohimbine is found a second alkaloid, *yohimbenine*, $C_{35}H_{45}N_3O_6$.

31. **Conessine** (*Wrightine*), $C_{24}H_{40}N_2$.—Contained as tannate in the bark and seeds of *Wrightia antidysenterica* R. Br. of *Holarrhena africana* DC., and of *H. antidysenterica* Wall. (Apocynaceæ). Needles, melting at 122°; may be sublimed. Diacid and bitertiary base.

32. **Alkaloids from the Seeds of the Stavesacre** (*Delphinium Staphisagria* L., Ranunculaceæ):

Delphinine, $C_{22}H_{35}NO_6$. Plates. Melting-point 120°. Inactive. Very poisonous; in physiological action resembles veratrine and aconitine. A weak base.

Delphinoidine, $C_{25}H_{42}NO_4$. Amorphous. Melting-point 110–120°. Inactive.

Delphisine, $C_{27}H_{46}N_2O_4$. Crystals, melting at 189°.

Staphisagrine, $C_{22}H_{33}NO_5$. Amorphous. Melting-point near 90°. Inactive.

33. Alkaloids from the Root of the Yellow Jasmine (*Gelsemium sempervirens* Pers., Apocynaceæ).

Gelsemine, $C_{24}H_{28}N_2O_4$. Crystals, melting at 45°; soluble in alkalies. Strong, monacid base, very poisonous.

Gelseminine, $C_{22}H_{26}N_2O_3$. Crystallizes. Melting-point 172°. Monacid, tertiary base, soluble in alkalies. Contains no methoxyl group.

34. Paucine, $C_{27}H_{39}N_5O_5+6\frac{1}{2}H_2O$.—In Pauco-nuts, the fruit of *Pentaclethra macrophylla* Benth. (Leguminosæ). Yellow leaflets, melting at 126°; soluble in water and alkalies. Diacid base. Is decomposed by concentrated hydrochloric acid or caustic soda into dimethylamine and pyridine bases.

35. Erythrophleïne, $C_{28}H_{43}NO_7$ or $C_{28}H_{45}NO_7$.—In the root of *Erythrophlœum guinense* Dow. (Leguminosæ). Crystalline, very poisonous, producing effects similar to those resulting from the action of digitalin. Is decomposed by concentrated hydrochloric acid into methylamine and an acid, *erythrophleïc* acid, $C_{27}H_{38}O_7$.

36. Alkaloids from the Seeds of *Vicia sativa* L. and *Vicia Faba minor* (Leguminosæ).

Vicine, $C_{28}H_{51}N_{11}O_{21}$ or $(C_8H_{15}N_3O_6)$. Is found in beet-root. Needles, soluble in dilute alkali. Boiling with dilute sulphuric acid effects decomposition into ammonia, a sugar, and the so-called *divicine*. Fusion with caustic potash gives rise to ammonia and potassium cyanide.

Convicine, $C_{10}H_{15}N_3O_7+H_2O$. Leaflets. By the action of mineral acids alloxantin is formed.

37. Emetine, $C_{30}H_{40}N_2O_5$ or $C_{30}H_{44}N_2O_4$.—In the root of the ipecacuanha (*Cephaelis Ipecacuanha* Wild., Rubiaceæ). Amorphous powder. Melting-point 70°. Acts as an emetic. Diacid, bitertiary base, optically inactive. Contains a hydroxyl and four methoxyls. Is decomposed by caustic potash into ammonia and quinoline bases.

With emetine apparently occur two other alkaloids, *cephaeline*, $C_{28}H_{40}N_2O_4$, and *psychotrine*.

38. **Lycopodine,** $C_{32}H_{52}N_2O_3$.—In *Lycopodium complanatum* L. (Lycopodiaceæ). Prisms, melting at 114–115°. Diacid base.

39. **Imperialine,** $C_{35}H_{60}NO_4$.—In the bulbs of *Fritillaria imperialis* L. (Liliaceæ). Needles, melting at 254°. Lævorotatory.

40. **Ergotinine** (*ecboline*), $C_{35}H_{40}N_4O_6$.—In ergot. Prisms, soluble in excess of alkali. In aqueous solution gives a violet fluorescence. A weak, monacid base, dextrorotatory. Acts as a hemostatic.

41. **Taxine,** $C_{37}H_{53}NO_{10}$.—In the seed and leaves of the yew (*Taxus baccata* L., Coniferæ). Amorphous powder. Melting-point 82°. Tertiary base. Narcotic.

42. **Solanine,** $C_{42}H_{75}NO_{15}$ or $C_{42}H_{75}NO_{12}$.—In the berries of the common nightshade (*Solanum nigrum* L., Solanaceæ); in the woody nightshade (*S. Dulcamara* L.); in the young shoots of the potato (*S. tuberosum* L.). Lustrous needles, melting at 235°. A very weak base, somewhat poisonous. Contains no methoxyl, but six hydroxyls. Hydrolysis with dilute acids gives rise to sugars and *solanidine,* $C_{41}H_{71}NO_2$.

Solanidine is also found with solanine in the plant. Solanine as ordinarily obtained is probably a mixture of both these alkaloids.

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